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Selected Abstracts
on

TRANSLOCATION AND AMPLIFICATION OF ONCOGENES

Peter C. Nowell, M.D.
Consulting Reviewer

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TABLE OF CONTENTS

INTRODUCTION.....	PAGE IV..... v-IV
EDITORIAL COMMENTARY.....	V..... vi-V
ABSTRACTS	ABSTRACT NUMBER
I. CHROMOSOMAL TRANSLOCATIONS AND DNA REARRANGEMENTS INVOLVING ONCOGENES	
A. Myc Oncogene Translocations	
1. Myc Translocations in Burkitt's Lymphoma.....	1-57
2. Myc Translocations in Murine Plasmacytomas.....	58-90
3. Myc Translocations Occurring in Other Lymphomas, Leukemias, and Neoplastic Cells.....	91-104
4. Reviews of Myc Translocations.....	105-136
B. Abl Oncogene Translocations	
1. Abl Translocations and Chronic Myelogenous Leukemia.....	137-171
2. Reviews of Abl Translocations.....	172-179
C. Translocations Involving Other Oncogenes	
1. Translocations Near or Involving the Sis Oncogene.....	180-188
2. Translocations Near or Involving Ras Oncogenes.....	189-194
3. Translocations Near or Involving the Mos Oncogene.....	195-201
4. Translocations Near or Involving Other Oncogenes.....	202-241
D. Reviews and General Studies of Oncogenes Associated with Translocations.....	242-266
II. AMPLIFICATION OF ONCOGENES	
A. Amplification of Myc Oncogenes	
1. Amplification of the C-myc Oncogene.....	267-308
2. Amplification of N-myc and L-myc Oncogenes.....	309-330
B. Amplification of Ras Oncogenes.....	331-354
C. Amplification of Other Oncogenes.....	355-377
D. General Studies and Reviews of Oncogene Amplification.....	378-395
III. GENERAL REVIEWS OF ONCOGENIC TRANSFORMATION BY ONCOGENE TRANSLOCATION OR AMPLIFICATION.....	396-424
SUBJECT INDEX.....	S-1
AUTHOR INDEX.....	A-1

INTRODUCTION

This ONCOLOGY OVERVIEW on translocation and amplification of oncogenes includes abstracts selected from the CANCERLIT database referencing articles published mainly from 1982 to mid-1986. The last CANCERLIT update searched for this ONCOLOGY OVERVIEW was June, 1986.

THE STRATEGY USED TO RETRIEVE THESE ABSTRACTS CAN BE REQUESTED FROM THE CIDAC-CCB AND ENTERED ON ANY MEDLARS/MEDLINE TERMINAL SYSTEM TO UPDATE REFERENCES IN THIS AREA.

The scope of this ONCOLOGY OVERVIEW encompasses only those chromosomal translocations, DNA rearrangements or gene amplifications involving known oncogenes or putative proto-oncogenes. A variety of oncogenes are covered in depth. These include myc, abl, ras, sis, and mos. However, any oncogene or similar transformation-related gene that may be near to or involved in a translocation or amplification is considered to be within scope. Several reviews and general studies which summarize data and speculate on mechanisms of oncogenic transformation are included. General chromosomal deletions and translocations are not covered, nor are rearrangements of virally derived sequences. A previous ONCOLOGY OVERVIEW entitled "Rearrangements of DNA Sequences as They Occur in Nature: Potential Models for Differentiation and Tumorigenesis" (OB-83/04) (1983) covers earlier citations.

This OVERVIEW was prepared by Gerald S. Kuncio, Ph.D., Subject Specialist for the CIDAC for Carcinogenesis and Cancer Biology, Information Ventures, Inc., Philadelphia, PA. Peter C. Nowell, M.D. of the University of Pennsylvania was the Consulting Reviewer and wrote the Editorial Commentary.

EDITORIAL COMMENTARY

The studies of chromosomes of neoplastic cells have provided significant contributions to our understanding of tumor biology over the past several decades. Recently, very rapid progress has been made as cytogenetic techniques have improved and investigations have been extended to the molecular level. With the development of better staining methods, it has been recognized that specific alterations in chromosomes are, associated with various degrees of constancy, common to with specific disorders (1,2). It has been hypothesized that these nonrandom karyotypic changes indicate sites in the genome where genes important in carcinogenesis may be located.

In some instances the consistent abnormality has been the gain or loss of a whole or parts of a chromosome, suggesting a critical role for gene dosage in oncogenesis (1,2). Other cytogenetic alterations have recently been identified as gene amplification units. These may appear as elongated homogeneously staining regions (HSRs), small extra-chromosomal paired chromatin bodies (double minutes, DMs), and abnormally banded regions (ABRs) (3). The most extensively investigated changes, however, have been specific reciprocal chromosome translocations, without apparent gain or loss of genetic material. It is theorized that their importance in carcinogenesis may result from position effects, with the translocation bringing an inactive (proto) oncogene into juxtaposition with activating sequences elsewhere in the genome (4).

This compilation of abstracts includes recent data supporting this hypothesis, primarily from studies of hematopoietic tumors, and also evidence that cytogenetic identification of gene amplification units can provide important clues to oncogene involvement in human neoplasia.

The most extensive work to date concerning the activation of a human proto-oncogene by chromosome translocation has come from studies on Burkitt's lymphoma. In most cases of this tumor there is a reciprocal translocation between chromosomes 8 and 14. In a minority there are variant translocations involving chromosomes 8 and 22 or chromosomes 2 and 8. In all instances the breakpoint in chromosome 8 is the same, the terminal portion of the long arm (band q24). The genes for the human immunoglobulin heavy and light chains have been mapped to chromosome regions involved in these translocations: the heavy chain locus to band 14q32, the lambda light chain genes to band 22q11, and kappa light chain genes to band 2p11. At the same time, the human homologue of the retroviral v-myc oncogene was mapped to the terminal portion of 8q, suggesting that this gene, as well as the immunoglobulin genes, could be significant in the pathogenesis of Burkitt's lymphoma (5).

This possibility has now been investigated in several laboratories (5-7). It has been demonstrated that in each of these translocations a transcriptionally active and rearranged immunoglobulin gene is brought into juxtaposition with the c-myc gene, resulting in deregulation of the oncogene. In the case of common t(8;14) translocation, the immunoglobulin heavy chain locus is split, and the c-myc oncogene, with or without structural alteration, is brought into association with it. In the variant translocations, the kappa or lambda immunoglobulin gene is translocated to the 3' end of the c-myc oncogene, which remains on chromosome 8, usually without structural alteration.

These various rearrangements are still being investigated, but it appears in each instance that the c-myc proto-oncogene comes under the influence of enhancers in

or adjacent to the immunoglobulin loci, resulting in deregulation of expression of the oncogene. Similar results in experimental lymphoid tumors of mice and rats support this conclusion (8).

The c-myc gene product is a nucleoprotein, apparently having a normal function in growth regulation of lymphocytes and other cells. Studies of the translocated c-myc gene, on the 14q+ chromosome of Burkitt tumor cells, indicate that it can still be regulated in another cellular background (e.g., a fibroblast). But when under the influence of an enhancing element in a B cell that is at the proper stage of differentiation, it does not respond to normal regulatory mechanisms (5). These findings concerning the c-myc gene in Burkitt's lymphoma have provided strong evidence for tumorigenic effects of a structurally unaltered but deregulated oncogene. However, the exact role of the myc gene product in the pathogenesis of Burkitt's lymphoma remains uncertain, as well as the contribution of other factors such as chronic infection with malaria and the Epstein-Barr virus.

With respect to other B cell tumors, a significant proportion have characteristic translocations that also involve the immunoglobulin heavy chain region of 14q (band q32) (1,2), although the "donor" site is different from that of the Burkitt tumor, being on either the long arm of chromosome 11 (q13) or the long arm of chromosome 18 (q21). Neoplastic cells from patients with B cell tumors having either a t(11;14) (q13;q32) translocation or a t(14;18) (q32;q21) translocation have recently been used to molecularly clone the chromosome breakpoints involved (9,10). They were found to be clustered in short segments either on chromosome 11 or chromosome 18, and the breakpoint on chromosome 14 was consistently within the immunoglobulin heavy chain locus. These findings have suggested that previously unknown oncogenes, located on chromosomes 11 and 18, may be involved in these rearrangements in a manner analogous to the c-myc gene in the t(8;14) translocation.

These two putative new oncogenes, tentatively named bcl-1 and bcl-2, are currently being characterized in several laboratories (9-12). Neither is homologous to any known oncogene. The findings to date indicate that in both cases the translocation is into the J region of the immunoglobulin locus on chromosome 14. The bcl-2 gene probe has been used to identify a characteristic 6 kilobase (kb) RNA transcript, and levels of this transcript in leukemic cells with the t(14;18) translocation are higher than in neoplastic B cells without it, suggesting deregulation of the bcl-2 gene (10). These preliminary findings indicate that molecular investigation of non-random chromosomal translocations in various tumors may help to identify human oncogenes that have not been previously recognized in the retroviral repertoire or through transfection assays.

Similar studies are now being extended to T cell neoplasms, with results suggesting that mechanisms similar to those in B cell neoplasms may be operating. The genes coding for several chains of the T cell antigen receptor have been mapped, and translocations involving those chromosomal regions have been reported in various T cell tumors (13-15). The gene for the alpha subunit of the T cell receptor has been mapped to chromosome 14 (band 14q11) (16), a site frequently involved in translocations and inversions in T cell tumors (14); the beta chain gene has been mapped to the terminal portion of 7q (band 7q35); and the gamma chain gene appears to be located at 7p13 (17,18). In a group of acute T cell leukemias of childhood, with a characteristic T(11;14) (p13;q11) translocation, it has been shown that the breakpoint on chromosome 14 does indeed interrupt the alpha locus of the T cell receptor (19). This translocation does not involve a known oncogene, but several cases of T cell leukemia have also been studied in which there is a t(8;14) (q24;q11) translocation involving the c-myc proto-oncogene. In these cases, the chromosomal rearrangement apparently brings the constant portion of the T-alpha receptor gene into juxtaposition with the c-myc gene on chromosome 8, resulting in deregulation of the oncogene (20). Although still very preliminary, these data sug-

gest that at least one of the T cell receptor genes may have the same "activating" role in T cell neoplasms as do the immunoglobulin genes in B cell tumors.

Among the nonlymphocytic leukemias, the only entity that has been extensively studied with respect to oncogene involvement is the characteristic t(9;22) (q34;q11) translocation that produces the Philadelphia chromosome in most typical cases of chronic myelogenous leukemia (CML) (1,2). Mapping of the chromosomal breakpoints in this translocation has indicated that the c-abl proto-oncogene is regularly translocated from its normal site on chromosome 9 to a very restricted region on chromosome 22. The term breakpoint cluster region (bcr) has been applied to this critical region (21).

Detailed study of the translocated c-abl oncogene in CML has demonstrated production of a novel 8 kb mRNA, larger than the normal transcript. Cloning of the joining region on chromosome 22 has now shown that the altered RNA is in fact a hybrid molecule containing both bcr and abl sequences (22). Furthermore, this transcript appears to code for an abnormal protein of high molecular weight possessing tyrosine kinase activity which has not been demonstrated with the normal product. Unlike the Burkitt tumor translocations, where the myc gene product appears unaltered, these findings in CML demonstrate a tumorigenic chromosomal translocation with an oncogene product that is modified in both structure and function.

Additional studies have indicated that, although translocations involving the same band of chromosome 22, band q11, are observed in cases of acute lymphocytic leukemia with a Philadelphia chromosome, in Ewing's sarcoma, and in certain variant cases of Burkitt's lymphoma, the breakpoints are heterogeneous at the molecular level and do not involve the bcr (23). Chromosomal translocations may thus identify possible sites of oncogene involvement, but detailed molecular characterization is required for confirmation.

This has certainly proved to be the case in initial attempts to demonstrate specific oncogene involvement in the spectrum of acute nonlymphocytic leukemias. For instance, it has been suggested that the c-erbA and p53 oncogenes, as well as others, could be significantly involved in the t(15;17)(q22;q21) translocation characteristic of acute promyelocytic leukemia. A similar relationship has been postulated for the c-mos oncogene and the t(8;21)(q22;q22) translocation seen in a subgroup of acute myelogenous leukemias. In several cases, such as c-mos and p53, the original gene mapping was erroneous, and the translocation breakpoints have proved to be far from the actual location of the oncogene. In other instances, detailed molecular study of the involved genes and their expression has not been completed, and one or more specific relationships may be demonstrated before this summary is published. In any event, it is certain that over the next few years additional important information will be forthcoming concerning chromosomal translocations and related oncogenes in hematopoietic tumors, and also in solid neoplasms of man and experimental animals.

The other type of chromosomal change in neoplastic cells that has been most definitely linked to alterations in oncogene function are the gene amplification units that appear as HSRs, DMs, and ABRs. In earlier studies of cell lines, it was demonstrated that these cytogenetic structures represented, in some cases, multiple copies of genes necessary for cell growth under specific culture conditions, and also that they may be relatively labile alternative forms of gene amplification (3,24,25). Although these structures do not demonstrate the same consistent localization within the genome as the nonrandom translocations, in some instances they have been shown to involve human homologues of retroviral oncogenes.

In general, such gene amplification units have been more commonly recognized in solid tumors than in hematopoietic neoplasms. This has been particularly true in neuroblastoma (26,27) where amplification of c-myc has been reported, as well as a homologous gene, now called N-myc, located on chromosome 2 (26). Furthermore, it has recently been shown that multiple copies of the N-myc gene are characteristically associated with more aggressive stages of neuroblastoma, indicating a role in

VII

tumor progression of this disease (28). In other solid tumors, including small cell lung carcinoma and other epithelial malignancies, amplification of c-myc, N-myc, and another variant, dubbed L-myc, has been reported, as well as amplification involving various members of the ras gene family (8,29). In many instances, this amplification has been associated with more aggressive stages of the disease, similar to neuroblastoma. These initial findings lead to the interesting speculation that among the various mechanisms for altering oncogene function, chromosome translocations are particularly relevant in later phases.

The same can be said about other mechanisms of oncogene alteration, not covered in these abstracts. At the cytogenetic level, gains and losses of single copies of individual chromosomes or segments of chromosomes are clearly important, but the specific genes involved and the nature of their abnormal function has not been clarified. Other studies have shown that submicroscopic forms of somatic genetic alteration, such as point mutation and promoter insertion, can also be critical in certain carcinogenic pathways. For any specific neoplasm, it may be necessary to identify a series of genetic alterations and multiple host factors that interact and ultimately lead to clinical disease. Despite these complexities, this series of abstracts makes it clear that further investigation at the molecular genetic level of the non-random chromosome abnormalities in human and experimental tumors represents a profitable and rapidly expanding approach to improved understanding of the pathogenesis of neoplasia.

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✓111

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ABSTRACTS

I.

CHROMOSOMAL TRANSLOCATIONS AND DNA REARRANGEMENTS INVOLVING ONCOGENES

A.

MYC ONCOGENE TRANSLOCATIONS

1.

Myc Translocations in Burkitt's Lymphoma

1. ALTERNATIVE INVOLVEMENT OF TWO CYTOGENETICALLY DISTINGUISHABLE BREAKPOINTS ON CHROMOSOME 8 IN BURKITT'S LYMPHOMA ASSOCIATED TRANSLOCATIONS

Manolova G, Manolova Y, Klein G, Lenoir G, Levan A

Institute of Oncology, Sofia, Bulgaria.

Cancer Genet Cytogenet; 20(1-2):95-9 1986

The chromosomes of 16 Burkitt's lymphoma (BL) derived cell lines were submitted to high-resolution G-bend analysis. They included seven lines with t(8;14), three with t(2;8), and four with t(8;22). The translocation breakpoint in chromosome 8 was located in 14q32.3, in chromosome 14 in 2p11.1, and in chromosome 2 in 22q12.12. In chromosome 8, the translocation breakpoint was located in two cytogenetically distinct subbands: 8q24.1 in cell lines with t(8;14) and t(2;8) and 8q24.22 in cell lines with t(8;22). In the light of recent molecular findings, these results indicate that the distance between the c-myc gene, located in 8q24, and the Ig sequences might be much larger in BL lines with t(8;22) than in those with t(2;8).

2. TRUNCATION OF EXON 1 FROM THE C-MYC GENE RESULTS IN PROLONGED C-MYC MRNA STABILITY

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Ludwig Institute for Cancer Research, MRC Centre, Cambridge, UK

EMBO J; 4(13B):3727-33 1985

The human c-myc gene consists of three exons transcribed from two distinct promoters and the function of the first noncoding exon is unknown. In COLO 320 cells, there co-exist normal and truncated (i.e., lacking exon 1) c-myc genes, both of which are transcribed. Studies on the turnover of c-myc mRNA show that the normal mRNA has an in vivo half-life of approximately 30 min which is approximately similar to the turnover time of the mRNA in lymphoblastoid cells. However, the truncated mRNA was found to be substantially more stable. This observation was also made with a Burkitt's lymphoma cell line which has a translocated, truncated c-myc gene. Therefore truncation of the c-myc gene can cause the mRNA to be more stable than the full size product suggesting that this can be a crucial factor in the activation of the c-myc oncogene, by exon 1 loss, in chromosomal translocation. The results also suggest a role for exon 1 in the c-myc mRNA degradative mechanism.

3. SUPPRESSION OF THE NORMAL MOUSE C-MYC ONCOGENE IN HUMAN LYMPHOMA CELLS

Fo S, ar-Rushdi A, Huebner K, Finan J, Nowell PC, Clarkson B, Croce CM

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Nature; 313(6002):493-5 1985

In Burkitt's lymphoma, which carries the t(8;14) chromosome translocation, the c-myc oncogene normally located on band 24 of human chromosome 8 (refs 1-3) translocates to the heavy-chain locus on chromosome 14 (refs 1, 4, 5); this results in transcriptional deregulation of the translocated c-myc oncogene, which is transcribed constitutively at elevated levels, while the normal c-myc oncogene on the uninvolved chromosome 8 is either silent or expressed at very low levels (A et-R. and C.M.C., unpublished results). We have now introduced the active c-myc oncogene of proliferating mouse spleen cells into human lymphoma cells carrying the t(8;14) chromosome translocation by hybridization, and have examined the hybrids for expression of the human and murine c-myc oncogene. The results of this analysis, reported here, indicate that the active mouse myc gene is shut off at the transcriptional level in the human lymphoma cells, implying that human B cells at the stage of differentiation of lymphoma cells used in this study are nonpermissive for normal c-myc transcription.

4. CLONING AND SEQUENCING OF A C-MYC ONCOGENE IN A BURKITT'S LYMPHOMA CELL LINE THAT IS TRANSLOCATED TO A GERM LINE ALPHA SWITCH REGION

Shouw LC, Ballantine M, Nishikura K, Erikson J, Kaji H, Croce CM

Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania 19104.

Mol Cell Biol; 5(3):501-9 1985

We have cloned and sequenced the translocated c-myc gene from the Burkitt's lymphoma CA46 cell line that carries a reciprocal translocation between chromosomes 8 and 14. The breakpoint lies within the first intron of c-myc, so that the first noncoding exon of the gene remains on the 8q chromosome. The second and third coding exons are translocated to the 14q+ chromosome into the switch region of C-alpha 1. The orientation of the c-myc gene with relationship to alpha 1 is 5' to 5', with directions of transcription in opposite orientation. DNA sequencing studies predict five changes in the amino acid sequence of the myc protein, two of which occur in a region within the second exon which is highly conserved in evolution. Southern blotting data indicate that the first exon of c-myc is rearranged 3' to 3' with the pseudo-epsilon gene. Because CA46 cells contain two rearranged mu genes, the translocation must have occurred after immunoglobulin rearrangement. The position of the breakpoint in CA46 occurs within a 20-base-pair region of the first intron of c-myc to which breakpoints have been mapped for two additional B-cell lymphomas with the t(8;14) translocation, ST486 and the Manca cell line. The region of the heavy chain locus to which c-myc has translocated is different in each case. Comparisons have been made of the levels of transcripts of the translocated c-myc gene in ST486 and CA46,

where the gene is not associated with the heavy chain enhancer, with its expression in the Manca cell, in which it is. The c-myc gene is transcribed at similar levels in all three cases.

5. THE TRANSLOCATED C-MYC ONCOGENE OF RAJI BURKITT LYMPHOMA CELLS IS NOT EXPRESSED IN HUMAN LYMPHOBLASTOID CELLS

Nishikura K, Erikson J, ar-Ru'aida A, Huebner K, Croce CM
Wistar Institute of Anatomy and Biology, Philadelphia, PA 19104
Proc Natl Acad Sci USA; 82(9):2900-4 1985

We hybridized Raji Burkitt lymphoma cells, which carry a t(8;14) chromosome translocation, with human lymphoblastoid cells to study the expression of the translocated cellular myc oncogene (c-myc) in the hybrid cells. In Raji cells the c-myc oncogene is translocated to a switch region of the gamma heavy chain locus (S gamma). Because of sequence alterations in the 5' exon of the translocated c-myc oncogene in this cell line, it is possible to distinguish the transcripts of the translocated c-myc gene and of the normal c-myc gene. S1 nuclease protection experiments with a c-myc first exon probe indicate that Raji cells express predominantly the translocated c-myc gene, while the level of expression of the normal c-myc gene is less than 2% of that of the translocated c-myc gene. Somatic cell hybrids between Raji and human lymphoblastoid cells retain the lymphoblastoid phenotype and express only the normal c-myc oncogene. This result indicates that the activation of a c-myc oncogene translocated to a S region depends on the stage of B-cell differentiation of the cells harboring the translocated c-myc gene and not on alterations in the structure of the translocated c-myc oncogene.

6. COEXPRESSION OF TRANSLOCATED AND NORMAL C-MYC ONCOGENES IN HYBRIDS BETWEEN DAUDI AND LYMPHOBLASTOID CELLS

Croce CM, Erikson J, Huebner K, Nishikura K
Wistar Institute, Philadelphia, Pennsylvania
Science; 227(4691):1235-8 1985

Mechanisms that affect the transcription of the c-myc oncogene take part in the development of B-cell neoplasias such as Burkitt's lymphoma. Daudi Burkitt lymphoma cells, which express only the translocated c-myc oncogene, were hybridized with human lymphoblastoid cells, which express the normal c-myc gene; the hybrids were phenotypically lymphoblastoid and expressed both the translocated and the normal c-myc gene. This result contrasts with the findings that the decapitated c-myc gene, translocated to an immunoglobulin switch mu or alpha region, is transcriptionally silent in lymphoblastoid hybrids. Thus, there may be at least two distinct enhancer-like elements capable of deregulating c-myc transcription in lymphomas and leukemias with t(8;14) chromosome translocations. In addition, since the Daudi X lymphoblastoid hybrids express both the translocated and the normal c-myc gene, the c-myc gene product does not autoregulate c-myc transcription.

7. STRUCTURAL ANALYSIS OF BOTH PRODUCTS OF A RECIPROCAL TRANSLOCATION BETWEEN C-MYC AND IMMUNOGLOBULIN LOCI IN BURKITT LYMPHOMA

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Nucleic Acids Res; 13(6):2141-52 1985

The balanced translocations that occur between the c-myc and immunoglobulin loci in Burkitt lymphoma provide an unusual opportunity to analyze both products of a reciprocal

recombination. Accordingly, we have determined the structure of the two reciprocal products of a translocation that joins the 5' portion of the c-myc gene on chromosome 8 to the immunoglobulin mu switch recombination signal on chromosome 14. By determining the nucleotide sequences at the translocation crossover points of both product chromosomes, we precisely locate these points with respect to nearby genes. This determination allows us to conclude that translocation involves nonhomologous recombination, is highly conservative of c-myc sequences (deleting only 16 bp at the crossover point), but deletes over 2 Kb of immunoglobulin sequences from the mu switch signal. The mu constant and c-myc genes are joined head-to-head about 3 Kb apart, while the IgH enhancer and an aberrantly rearranged D/J region are linked to sequences 5' of c-myc on the reciprocal product.

8. CHROMATIN STRUCTURE OF THE HUMAN C-MYC ONCOGENE: DEFINITION OF REGULATORY REGIONS AND CHANGES IN BURKITT'S LYMPHOMAS

Siehmhus U, Hennighausen L, Basset J, Leder P
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Hematol Bluttransfus; 29:261-5 1985

Keywords (MeSH): Alleles; Burkitt's Lymphoma/*familial and genetic/ultrastructure; Chromatin/*ultrastructure; Deoxyribonuclease I; DNA Restriction Enzymes; DNA, Neoplasm/genetics; *Genes, Regulator; Human; *Oncogenes; Translocation (Genetics).

9. CHROMATIN STRUCTURE AROUND THE C-MYC GENE IN BURKITT LYMPHOMAS WITH UPSTREAM AND DOWNSTREAM TRANSLOCATION POINTS

Dyson PJ, Rabbitts TH
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Proc Natl Acad Sci USA; 82(7):1984-8 1985

Burkitt lymphoma cells seem to have abnormal c-myc gene activity resulting from chromosomal translocation. We have examined the consequences of translocation on putative control sequences near to the c-myc gene by DNase I hypersensitivity mapping of chromatin. There is no detectable difference in the pattern of hypersensitivity (compared with the actively transcribed c-myc gene of lymphoblastoid cells) in Burkitt lymphoma cells where the translocation point occurs at a considerable distance upstream or downstream of c-myc. When the translocation occurs near the 5' end of the c-myc gene, resulting in loss of hypersensitive sites, those that remain show the same sensitivity as in lymphoblastoid cell lines. We conclude that translocation has little general effect on the usual pattern of hypersensitive sites near to the c-myc gene but new sites can be observed in some cases in the immunoglobulin region near to the breakpoint. These may be sites normally involved in immunoglobulin gene transcription and may exert a subtle effect on the translocated c-myc gene.

10. CHROMATIN STRUCTURE OF TRANSCRIPTIONALLY ACTIVE AND INACTIVE HUMAN C-MYC ALLELES

Dyson PJ, Littlewood TD, Forster A, Rabbitts TH
Ludwig Institute for Cancer Research, MRC Centre, Cambridge, UK.
EMBO J; 4(11):2885-91 1985

To help elucidate the mechanism of regulation of the c-myc gene we have characterised the DNase I hypersensitive sites around this gene in the human promyelocytic leukaemia cell line HL60, which carries amplified c-myc, and in Ramos, a Burkitt's lymphoma cell line with a translocation close to

exon 1 of c-myc. Although dividing HL60 cells display a pattern of DNase I hypersensitive sites which is similar to that of previously described c-myc genes in B cells (lymphoblastoid and Burkitt's lymphoma), changes were found in DNase I hypersensitive sites upon differentiation of the HL60 cell line (accompanied by decreased c-myc transcription). Lack of c-myc transcription coincides with the loss of several DNase I hypersensitive sites and the reduction in intensity of a further site. A similar pattern was also seen in the inactive allele of the Burkitt's lymphoma cell line Ra-nos. A striking feature of both differentiated HL60 cells and of the inactive allele in Ramos is the quantitative maintenance of a DNase I hypersensitive site which occurs approximately 2.5 kb upstream of the c-myc gene promoters.

11. DISCUSSION ON THE METABOLISM OF C-MYC MRNA AND PROTEIN

Rabbitts TH, van Straaten P, Rabbitts PH, Watson J
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Proc R Soc Lond [C] 226(1242):79-82 1985

The c-myc gene is expressed in a variety of actively growing cells and tissues including lymphoblastoid cell lines made in vitro by EBV infection (Hamlyn and Rabbitts 1983). The gene is implicated in the derivation of Burkitt's lymphoma because of its association with consistent chromosomal translocations (Dalla-Favera et al. 1982; Neel et al. 1982; Taub et al. 1982) and in, for example, some colon carcinomas where the gene is amplified (Alitalo et al. 1983). To understand the formation of these cancers, we must determine the function of the c-myc protein in the cell. In this discussion we describe some features of c-myc metabolism which indicate that its expression may normally be strictly modulated; it is possible that the potential oncogenic effect of c-myc in various tumours is the result of loss of this ability to modulate its activity.

12. COORDINATED EXPRESSION OF C-MYC GENE AND A MULTIGENIC SET MAY MODULATE THE MALIGNANT PHENOTYPE IN HUMAN HAEMOPOIETIC CELL LINES

Harel J, Hanania N, Shaul D, Zelizerovski D, Castagna M
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Hematol Bluttransfus; 29:372-5 1985

Keywords (MeSH): Burkitt's Lymphoma/*familial and genetic/pathology; Cell Differentiation; Cell Division; Cell Line; *Cell Transformation, Neoplastic; Epstein-Barr Virus/genetics; Human; Leukemia, Myeloblastic; Lymphocytes/cytology; Nucleic Acid Hybridization; *Oncogenes; Phenotype; RNA, Neoplasm/genetics; Transcription, Genetic.

13. REARRANGEMENT OF THE PROTO-ONCOGENE C-MYC IN FRESH CELLS FROM BURKITT'S LEUKEMIA (L3)

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Nouv Rev Fr Hematol; 27(3):157-61 1985

The presence of a rearrangement of the proto-oncogene c-myc was investigated in the DNA of fresh cells isolated from the blood of two patients with Burkitt's leukemia (L3), and from the node biopsy of a patient with Burkitt's lymphoma. Both samples from the L3 leukemia patients had the characteristic t(8;14) translocation, while the lymphoma specimen presented no abnormality of chromosome 8. Only one of the leukemic DNA's presented a rearranged c-myc pattern, with the breakpoint region located between the first and the second exon. The c-myc pattern of the two other patients appeared normal. The finding of a rearranged c-myc oncogene in fresh cells from a Burkitt's leukemia is direct evidence for

the implication of c-myc in the disease whereas most of the rearrangements previously described have been found in cell lines established in culture.

14. BREAKAGE ON CHROMOSOME 2 BRINGS THE CK GENE TO A REGION 3' OF C-MYC IN A BURKITT'S LYMPHOMA LINE CARRYING A (2;8) TRANSLOCATION

Malcolm S, Davis M, Rabbitts TH
Biochemistry Department, Queen Elizabeth College, London, UK
Cytogenet Cell Genet; 37(3):168-72 1985

We have shown using in situ hybridization that the constant region of the kappa light chain immunoglobulin gene (Ck) is translocated from chromosome 2 to chromosome 8 in Burkitt's lymphoma cells with a (2;8) translocation. The Ck gene then ends up adjacent to and on the 3' side of c-myc. The breakpoint probably falls between the gene for the variable region of the kappa light chain (Vk) and the Ck gene.

15. MAPPING OF TRANSFORMING GROWTH FACTOR ALPHA GENE ON HUMAN CHROMOSOME 2 CLOSE TO THE BREAKPOINT OF THE BURKITT'S LYMPHOMA T(2;8) VARIANT TRANSLOCATION

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Cancer Res; 45(11 Pt 2):593-7 1985

Transforming growth factors (TGFs) are defined as biologically active polypeptides which reversibly confer the transformed phenotype onto untransformed cultured cells. TGF-alpha shows sequence homology with epidermal growth factor and competes with epidermal growth factor for binding to the epidermal growth factor receptor, stimulating the phosphorylation of the receptor. TGF-alpha is secreted by many transformed cells and may be involved in embryonic development. A cloned human TGF-alpha gene was used to map the locus for the TGF-alpha precursor to the short arm of human chromosome 2, region 2p11 - 2p13, by Southern blotting techniques with DNA prepared from rodent X human somatic cell hybrids. These hybrids contained different subsets of human chromosomes and included a set with a translocation between human chromosomes 1 and 2 [t(1;2)(q32;q13)]. In situ hybridization of the TGF-alpha probe to normal human metaphase spreads confirmed these data and localized TGF-alpha more precisely to bands 2p11 - 2p13. Breakpoints in the variant Burkitt lymphoma translocation t(2;8) occur within these bands. Such a t(2;8) translocation could place TGF-alpha next to c-myc in band 8q24. The possibility is raised that TGF-alpha might contribute to tumor progression in these cases of Burkitt's lymphoma.

16. THE 2P BREAKPOINT OF A 2;8 TRANSLOCATION IN BURKITT LYMPHOMA INTERRUPTS THE V KAPPA LOCUS

Emanuel BS, Selden JR, Chaganti RS, Jhanwar S, Nowell PC, Croce CM
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Proc Natl Acad Sci USA; 81(8):2444-6 1984

The majority of chromosomal rearrangements observed in Burkitt lymphomas involve a translocation between 8q and 14q, while the remaining minority carry variant translocations between chromosome 8 and either 2 or 22. We have studied the J1 Burkitt lymphoma cell line carrying the variant 2;8 chromosome translocation using a combination of high-resolution and molecular cytogenetic techniques. We have determined that the chromosome 2 breakpoint of the 2;8 translocation in these cells is in the distal portion of 2p11.2. In situ hybridization of a DNA probe for kappa light chain

variable (V kappa) region demonstrated that this 2p11.2 breakpoint is within the V kappa region. There was significant hybridization of the probe to both the 2p- and 8q+ chromosomes, with 23% of all grains considered to be specific for V kappa located over the middle one-third of the long arm of the 8q+ chromosome. Thus, there is translocation of the entire kappa constant (C kappa) region and a portion of the region carrying V kappa genes from 2p to a region 3' of the c-myc oncogene on the involved chromosome 8, resulting in transcriptional activation of the c-myc that is quite distant from the 5' end of the C kappa gene. These results provide direct evidence for translocation-related rearrangement of the kappa immunoglobulin gene cluster in this Burkitt lymphoma and for the assignment of the V kappa locus to 2p11.2.

17. REPRESSION OF REARRANGED MU GENE AND TRANSLOCATED C-MYC IN MOUSE 3T3 CELLS X BURKITT LYMPHOMA CELL HYBRIDS

Nishikura K, ar-Rushdi A, Erikson J, DeJesus E, Dugan D, Croce CM

Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania.

Science; 224(4647):399-402 1984

The productively rearranged immunoglobulin mu chain gene and the translocated cellular oncogene c-myc are transcribed at high levels both in human Burkitt lymphoma cells carrying the t(8;14) chromosome translocation and in mouse plasmacytoma X Burkitt lymphoma cell hybrids. In the experiments reported here these genes were found to be repressed in mouse 3T3 fibroblast X Burkitt lymphoma cell hybrids. Such repression probably occurs at the transcriptional level since no human mu- and c-myc messenger RNAs are detectable in hybrid clones carrying the corresponding genes. It is therefore concluded that the ability to express these genes requires a differential B cell environment. The results suggest that the 3T3 cell assay may not be suitable to detect oncogenes directly involved in human B cell oncogenesis, since 3T3 cells apparently are incapable of transcribing an oncogene that is highly active in malignant B cells with specific chromosomal translocations.

18. TRANSLOCATED C-MYC ONCOGENE OF BURKITT LYMPHOMA IS TRANSCRIBED IN PLASMA CELLS AND RERESSED IN LYMPHOBLASTOID CELLS

Croce CM, Erikson J, ar-Rushdi A, Aden D, Nishikura K
Wistar Institute of Anatomy and Biology, Philadelphia, PA.
Proc Natl Acad Sci USA; 81(10):3170-4 1984

We examined somatic cell hybrids between Burkitt lymphoma cells and either human lymphoblastoid cells or mouse plasmacytoma cells for the expression of the translocated c-myc oncogene. The results of this study indicate that the translocated c-myc oncogene is transcribed in plasma cells but is repressed in lymphoblastoid cells. Thus, the factors necessary for translocated c-myc transcription are present in plasma cells and Burkitt lymphoma cells but are absent or inactive in lymphoblastoid cells. Since the distance between the rearranged immunoglobulin loci and the c-myc oncogene can even exceed 30-50 kilobases, we speculate that the translocated c-myc oncogene is under the transcriptional control of enhancer-like elements capable of acting over long distances. The activity of this long-range enhancer may depend on the interaction with transacting factors that are active in plasma cells and in Burkitt lymphoma cells but are not active in lymphoblastoid cells. We also examined the transcription of the first exon of the c-myc oncogene, which becomes separated from the second and third exon because of the chromosomal break involving the first intron. This exon is transcribed at high levels in ST486 Burkitt lymphoma cells with the t(8;14)

chromosome translocation. Hybrids between lymphoblastoid and ST486 cells expressed high levels of transcripts of the first exon, whereas hybrids between plasma cells and ST486 cells did not. Thus, transcription of the separated first exon can be enhanced in lymphoblastoid and Burkitt lymphoma cells because of its close proximity to the heavy chain enhancer that is normally located between the joining and the switch region of the C mu gene. Such enhancement, however, does not occur in plasma cells, possibly because these cells are able to suppress completely the c-myc oncogene, unless it has been placed in the proximity of a rearranged immunoglobulin constant region gene.

19. BURKITT'S LYMPHOMA: CHROMOSOME TRANSLOCATIONS AND ONCOGENE ACTIVATION

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UT MD Anderson Clin Conf Cancer; 27:161-9 1984

In previous work, the use of somatic cell genetic techniques was found to allow the mapping of the genes for human immunoglobulin heavy chains to chromosome 14, of lambda light-chain genes to chromosome 22, and of kappa light-chain genes to chromosome 2; these findings suggested that the immunoglobulin chain genes might be involved in the translocations involving chromosomes 14, 22, and 2 observed in Burkitt's lymphoma. Furthermore, recent analysis of rodent-human hybrids for the presence of the human homologues of known retroviral oncogenes has allowed the localization of several human oncogenes, one of which, the so-called c-myc oncogene, is located on the terminal portion of the long arm of chromosome 8, suggesting that the c-myc oncogene might also have a role in the development of the Burkitt's tumor, since this long arm of chromosome 8 is the segment that translocates to chromosome 14 in the typical t(8;14) translocation. Using a combination of cytogenetic and somatic genetic techniques, the authors examined various aspects of the structure and function of the immunoglobulin genes and the c-myc oncogene in Burkitt's tumor cell lines having the usual t(8;14) translocation and also in those having the variant t(8;22) and t(2;8) rearrangements. The findings of the study supported the hypothesis that chromosomal translocations can be one means by which oncogenes can undergo alterations in function that result in a selective growth advantage for the cell bearing such a translocation, the progeny of that cell emerging as a neoplastic clone. Specifically, the findings in the Burkitt's tumor suggest that a chromosomal rearrangement in a B lymphocyte that places the c-myc oncogene adjacent to a transcriptionally active immunoglobulin gene leads to markedly increased transcription of the oncogene under circumstances in which it is not normally active.

20. THE TRANSLOCATED C-MYC ONCOGENE OF BURKITT LYMPHOMA IS DIFFERENTIALLY REGULATED IN LYMPHOBLASTOID VS PLASMA CELLS

Croce CM, Erikson J, ar-Rushdi A, Aden D, Nishikura K
Curr Top Microbiol Immunol; 113:133-45 1984

Keywords (MeSH): Animal; Burkitt's Lymphoma/*familial and genetic; Cell Line; *Chromosomes, Human, 13-15; *Chromosomes, Human, 6-12; DNA, Neoplasm/isolation and purification; Human; Hybrid Cells/physiology; Mice; Mutation; Nucleic Acid Hybridization; *Oncogenes; Plasmacytoma/familial and genetic; Transcription, Genetic; *Translocation (Genetics).

21. CLONING AND CHARACTERIZATION OF THE HUMAN C-MYC ONCOGENE

Watt RA
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Dis Abstr Int kBL: 44(12):3622-B 1984

Considerable evidence has accumulated to suggest that cellular oncogenes are involved in malignant transformation. c-myc, the c-onc gene corresponding to the v-onc gene of MC29 virus, has been implicated in the generation of chicken B-cell lymphomas, where the lymphoma appears to result from the integration of the avian leukosis provirus adjacent to, and transcriptional activation of, the host c-myc gene. c-myc has also been implicated in both human Burkitt lymphomas and murine plasmacytomas, where the activation of c-myc appears to result from translocations. (Author abstract)

22. THE EFFECT OF TRANSLOCATIONS ON THE CELLULAR MYC GENE IN BURKITT LYMPHOMAS

Mitchell KF, Battey J, Hollis GF, Moulding C, Taub R, Leder P
Department of Genetics, Harvard Medical School, Boston, Massachusetts
J Cell Physiol kSupplA: 3:171-7 1984

Chromosomal translocations are found to be a characteristic feature of Burkitt lymphomas. Similar translocations are found in mouse plasmacytomas and both diseases involve interchanges between one of the immunoglobulin loci and DNA in the vicinity of the myc gene. The structure of the myc gene has been elucidated from studies on translocated versions of the gene. Activation of the myc gene may play a role in transformation by promoting growth of the cells bearing the rearranged chromosomes. (40 Refs)

23. ACTIVATION AND SOMATIC MUTATION OF THE TRANSLOCATED C-MYC GENE IN BURKITT LYMPHOMA CELLS

Taub R, Moulding C, Battey J, Murphy W, Vasicek T, Lenoir GM, Leder P
Department of Genetics, Harvard Medical School, Boston, Massachusetts
Cell: 36(2):339-48 1984

In contrast to other human tumors in which the c-myc gene and its transcript are greatly amplified, careful analysis of t(8;14) Burkitt cell lines indicates that the c-myc transcript is marginally, and in some cases not at all, increased by comparison to control lymphoblastoid cell lines. Instead, there is a more subtle alteration in the expression of the translocated c-myc gene characterized by a shift in promoter utilization and an apparent insensitivity to the regulation that inactivates the normal c-myc allele within these same cells. In some Burkitt cell lines, such deregulation might be because of the loss of a putative control region through removal of the large dual promoter/leader segment of the c-myc gene. In other cell lines, however, this deregulation may be explained by somatic mutations that occur within the putative control region even though it is located many hundreds of bases from the translocation breakpoint.

24. A VARIANT TRANSLOCATION PLACES THE LAMBDA IMMUNOGLOBULIN GENES 3' TO THE C-MYC ONCOGENE IN BURKITT'S LYMPHOMA

Hollis GF, Mitchell KF, Battey J, Potter H, Taub R, Lenoir GM, Leder P
Department of Genetics, Harvard Medical School, Boston, Massachusetts
Nature: 307(5953):752-5 1984

Most translocations that occur in Burkitt's lymphoma involve movement of part of chromosome 8, containing the c-myc gene, from its normal position to the immunoglobulin heavy-chain locus on chromosome 14. The genes are often joined

at their 5' ends in opposite transcriptional directions. However, a significant minority of Burkitt translocations involve the light-chain loci on chromosome 2 (kappa) or 22 (lambda). We have characterized one of these from a European-derived cell line (IARC-BL37) that carries an 8;22 translocation. Here the translocation has joined the 5' portion of the lambda light-chain locus to the 3' portion of the c-myc gene at a position about 7 kilobases from the normal c-myc promoters. The translocation is reciprocal and relatively conservative, involving the loss of only 21 base pairs from the site of recombination. This translocation allows us to orient the lambda genes with respect to the centromere of chromosome 22 and to predict the orientation of other translocations involving these chromosomal segments. The 3' translocation is accompanied by an increased level of c-myc transcripts, especially that derived from a normally under-used c-myc promoter.

25. A NOVEL ALTERATION IN THE STRUCTURE OF AN ACTIVATED C-MYC GENE IN A VARIANT T(2;8) BURKITT LYMPHOMA

Taub R, Kelly K, Battey J, Latt S, Lenoir GM, Tantravabi U, Tu Z, Leder P
Department of Genetics, Harvard Medical School, Boston, Massachusetts
Cell: 37(2):511-20 1984

We have characterized a variant Burkitt lymphoma in which translocation joins the immunoglobulin kappa locus on chromosome 2 to the c-myc gene on chromosome 8. This Burkitt lymphoma is especially interesting because, in contrast to the more common lymphomas that carry 8;14 translocations, it carries a translocation that involves a light chain locus and occurs 3' to and at least 20 kb downstream of the c-myc gene. Furthermore, the c-myc gene from the translocated chromosome is abnormally expressed in that there is a characteristic shift in c-myc promoter utilization and an increase in c-myc transcript. These disturbances could be explained by novel structural alterations that occur in the c-myc gene and include a duplication of a 2.5 kb segment of DNA containing the two c-myc promoters and their untranslated leader exons. Interestingly, these alterations arise at a considerable distance from the translocation breakpoint.

26. CHROMATIN STRUCTURE AND PROTEIN BINDING IN THE PUTATIVE REGULATORY REGION OF THE C-MYC GENE IN BURKITT LYMPHOMA

Siebenlist U, Hennighausen L, Battey J, Leder P
Department of Genetics, Harvard Medical School, Boston, Massachusetts
Cell: 37(2):281-91 1984

A chromosomal myc gene displays one of three patterns of activity depending upon the arrangement of the gene and its allelic partner. In nonmalignant B cells both myc alleles are normally expressed. In Burkitt lymphoma cells carrying both a translocated and a nontranslocated myc allele, the translocated allele is inappropriately expressed, while the nontranslocated allele is virtually inactive. Here we examine the chromatin structure of these genes using DNAase I hypersensitivity in nonmalignant lymphoblastoid cells and in the Burkitt lymphoma, BL31. Three hypersensitivity patterns emerge that correlate with the state of the gene and reveal sites associated with putative regulatory structures. One region is associated with the two myc promoters, one with a specific nuclear protein binding site, and one - which is markedly enhanced in the inactive germline gene in the Burkitt cell - with a putative negative control region. The perturbation of the normal pattern in this particular Burkitt cell may be due to the action of an immunoglobulin enhancer.

27. CHROMATIN STRUCTURAL CHANGES IN THE PUTATIVE REGULATORY REGION OF C-MYC ACCOMPANY THE TRANSLOCATION IN A BURKITT LYMPHOMA

Sebenius U, Hennighausen L, Battey J, Leder P
Curr Top Microbiol Immunol; 113:183-9 1984

Keywords (MeSH): Alleles; Base Sequence; Burkitt's Lymphoma/*familial and genetic/immunology; Chromatin/*ultrastructure; Deoxyribonuclease I; Enhancer Elements (Genetics); *Genes, Regulator; Human; Immunoglobulins, Heavy Chain/genetics; Nucleic Acid Hybridization; *Oncogenes; Transcription, Genetic; *Translocation (Genetics).

28. CHROMOSOME TRANSLOCATION CAN OCCUR ON EITHER SIDE OF THE C-MYC ONCOGENE IN BURKITT LYMPHOMA CELLS

Davis M, Malcolm S, Rabbitts TH
Biochemistry Department, Queen Elizabeth College, London, UK.
Nature; 308(5956):286-8 1984

In Burkitt lymphoma cells reciprocal chromosomal translocations are observed between the long arm of chromosome 8 (8q24) and either the long arm of chromosome 14 (14q32), the short arm of chromosome 2 (2p12) or the long arm of chromosome 22 (22q11). Gene mapping studies have shown that c-myc, the cellular homologue of the viral myc oncogene, is localized at 8q24 (ref 3-5) and that the three immunoglobulin gene loci map at the breakpoints involved in the translocation: immunoglobulin heavy-chain genes are located at 14q32 (refs 6, 7), kappa light chains at 2p12 (ref. 8) and delta light chains at, or close to, 22q11 (ref 9, 10). This correlation suggests an association of immunoglobulin gene rearrangements with the occurrence of these specific translocations. By using in situ hybridization we have examined the translocation point with respect to c-myc in two cell lines containing 2;8 translocation, and report here that the c-myc gene remains on the chromosome 8 involved in the reciprocal exchange with chromosome 2. We have also confirmed that the c-myc gene moves from the translocated chromosome 8 in a cell line having a 8;14 translocation. These results show that chromosomal breakage can occur on either side of the c-myc gene in Burkitt lymphoma cells.

29. EFFECT OF SOMATIC MUTATION WITHIN TRANSLOCATED C-MYC GENES IN BURKITT'S LYMPHOMA

Rabbitts TH, Forster A, Hamlyn P, Baer R
MRC Laboratory of Molecular Biology, MRC Centre, Cambridge, UK.
Nature; 309(5969):592-7 1984

Our previous studies of a translocated c-myc gene in the Raji Burkitt's lymphoma cell showed somatic mutations in exons 1 and 2. We have extended these observations to two other translocated c-myc genes and find a common occurrence of mutation in the noncoding exon 1. We also found that in Raji cells, unlike other Burkitt's lymphoma cell lines, the normal allele of the c-myc gene is transcribed as well as the translocated gene. These results support a model in which c-myc oncogene activation in Burkitt's lymphoma occurs by disruption of a normal transcriptional control mechanism in which the c-myc protein is itself involved.

30. C-MYC GENE ACTIVATION AND CHROMOSOMAL TRANSLOCATION

Rabbitts TH, Baer R, Davis M, Forster A, Rabbitts PH, Malcolm S
Medical Research Council Laboratory of Molecular Biology, Cambridge, England.
J Cell Sci Suppl; 1:95-101 1984

Burkitt's lymphoma cells are characterized by the presence of specific chromosomal translocation bringing the immunoglobulin

and the c-myc proto-oncogenes into the proximity of each other. Different translocations involve each of the three immunoglobulin loci but the breakpoint with respect to the c-myc gene is shown to be very variable. In t(8;14) the breakpoint occurs upstream from the c-myc gene whilst in the variant lymphomas it occurs downstream from the gene. Possible ways in which the translocation affects the c-myc gene are discussed.

31. THE C-MYC GENE PARADOX IN BURKITT'S LYMPHOMA CHROMOSOMAL TRANSLOCATION

Rabbitts TH, Baer R, Davis M, Forster A, Hamlyn PH, Malcolm S
Curr Top Microbiol Immunol; 113:166-71 1984

Keywords (MeSH): Animal; Base Sequence; Burkitt's Lymphoma/*familial and genetic; Cell Transformation, Neoplastic; *Chromosomes, Human, 6-12; Human; Mice; Mutation; Nucleic Acid Hybridization; *Oncogenes; Plasmacytoma/familial and genetic; *Translocation (Genetics); Variation (Genetics).

32. ACTIVATED ONCOGENES IN BURKITT'S LYMPHOMA

Lenoir GM, Land H, Parada LF, Cunningham JM, Weinberg RA
Curr Top Microbiol Immunol; 113:6-14 1984

Keywords (MeSH): Animal; Burkitt's Lymphoma/*familial and genetic/microbiology; Cell Transformation, Neoplastic; Embryo; Epstein-Barr Virus/genetics/isolation and purification; Human; *Oncogenes; Rats; Translocation (Genetics).

33. ACTIVATION OF THE C-MYC ONCOGENE IN B AND T LYMPHOID TUMORS

Cory S, Gerondakis S, Corcoran LM, Bernard O, Webb E, Adams JM
Curr Top Microbiol Immunol; 113:161-5 1984

Keywords (MeSH): B Lymphocytes/*cytology; Base Sequence; Burkitt's Lymphoma/familial and genetic; *Cell Transformation, Neoplastic; Cloning, Molecular; Genes, Structural; Human; Immunoglobulins/genetics; Lymphoma/*familial and genetic/microbiology; *Oncogenes; Plasmacytoma/familial and genetic; Retroviridae/genetics; T Lymphocytes/*cytology; Translocation (Genetics).

34. ACTIVATION OF A TRANSLOCATED C-MYC GENE: ROLE OF STRUCTURAL ALTERATIONS IN THE UPSTREAM REGION

Wiman KG, Clarkson B, Hayday AC, Saito H, Tenevawa S, Hayward WS
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Proc Natl Acad Sci USA; 81(21):6798-802 1984

The translocated c-myc gene in AW-Ramos, a Burkitt lymphoma cell line carrying the 8;14 translocation, is expressed at 2- to 5-fold higher levels than c-myc in lymphoblastoid cell lines. The translocation event has joined c-myc to the IgM switch region. As a consequence, a recently identified immunoglobulin transcriptional enhancer element is not linked to the translocated c-myc gene. Chromosomal recombination occurs approximately equal to 340 nucleotides upstream of the c-myc 5' cap site, leaving all three c-myc exons intact. The nucleotide sequences of the two coding exons in the translocated c-myc gene are identical to those of the normal c-myc gene. Nucleotide sequence analyses of the first, non-coding c-myc exon and of the region between this exon and the chromosomal recombination point reveal two single-base differences from normal c-myc. Our data indicate that altered expression rather than an altered gene product is responsible for c-myc activation in AW-Ramos cells and that this is a result of either loss of regulatory sequences located greater

than 340 nucleotides upstream of c-myc or disruption of normal c-myc regulation by one or both base substitutions. Alternatively, unidentified enhancer-like sequences in the Ig locus may alter the expression of c-myc.

35. C-MYC AND IMMUNOGLOBULIN KAPPA LIGHT CHAIN CONSTANT GENES ARE ON THE 8Q+ CHROMOSOME OF THREE BURKITT LYMPHOMA LINES WITH T(2;8) TRANSLOCATIONS

Rappold GA, Hamster H, Cremer T, Adolph S, Henglein B, Freese UK, Lenoire GM, Bornhauss GW

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EMBO J; 3(12):2931-5 1984

We have determined the localization of c-myc and the immunoglobulin kappa light chain genes on the 8q+/2p- chromosomes of the three Burkitt lymphoma lines BL21, LY66 and LY91 with t(2;8) translocation by in situ hybridization. BL21 is characterized by a complex translocation in which a piece of chromosome 9 appears to be located between the fragments of chromosome 8 and 2 on the 8q+ chromosome. Our data indicate that in all three cell lines the c-myc gene is located on the 8q+ chromosome proximal to the breakpoint in band 8q24. In all cell lines examined the cluster of kappa variable genes has remained on the 2p- chromosome. In LY91 cells the major part of the joining region remained on 2p-, while the joining region has moved to 8q+ in the cell lines BL21 and LY66. In all three cell lines the constant kappa light chain gene was found on the 8q+ chromosome. The fact that an essentially identical pattern was found in the cell line BL21, with the complex translocation, suggests that the insertion of the piece of chromosome 9 into the 8q+ chromosome might be a secondary event. Our present data fit into the concept that in all Burkitt lymphoma lines investigated so far, including cases with t(8;14) and the variant translocations t(2;8) and t(8;22), the c-myc gene becomes situated at the 5' side of an immunoglobulin constant gene. This may have implications for the generation of somatic mutations in the coding and non-coding part of the c-myc gene.

36. STRUCTURE AND EXPRESSION OF THE ONCOGENE C-MYC IN FRESH TUMOR MATERIAL FROM PATIENTS WITH HEMATOPOIETIC MALIGNANCIES

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Mol Cell Biol; 4(6):1096-103 1984

C-myc is the cellular gene homologous to the transforming sequence of MC29, an acute avian retrovirus. The human c-myc gene was cloned and used to study the structure and expression of c-myc in a variety of human hematopoietic malignancies. In a careful study of 106 patients, c-myc RNA was found to be expressed at elevated levels in tumor cells of 17 leukemia patients and five lymphoma patients. The c-myc gene was found to be rearranged in two lymphomas, an African Burkitt's lymphoma and a non-Hodgkins lymphoma in leukemic phase. The Burkitt's rearrangement involved the insertion of new DNA sequences upstream from the c-myc 5' coding region, presumably replacing the normal c-myc transcriptional promoter. None of the other 104 patients, including 20 with elevated myc expression, exhibited any evidence of a genetic rearrangement involving the c-myc gene. Our results show that there is a subset of hematopoietic malignancies characterized by elevated expression of c-myc. This elevated expression in most cases is not due to obvious genetic changes (rearrangement, amplification) at the c-myc locus nor to chromosomal translocations in the vicinity of this gene.

37. TRANSLOCATION OF AN IMMUNOGLOBULIN KAPPA LOCUS TO A REGION 3' OF AN UNREARRANGED C-MYC ONCOGENE ENHANCES C-MYC TRANSCRIPTION

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Proc Natl Acad Sci USA; 80(24):7581-5 1983

We have studied somatic cell hybrids between mouse myeloma and JI Burkitt lymphoma cells carrying a t(2;8) chromosome translocation for the expression of human kappa chains. and for the presence and rearrangements of the human c-myc oncogene and kappa chain genes. Our results indicate that the c-myc oncogene is unrearranged and remains on the 8q+ chromosome of JI cells. Two rearranged C kappa genes were detected: the expressed allele on normal chromosome 2 and the excluded kappa allele that was translocated from chromosome 2 to the involved chromosome 8 (8q+). The distribution of V kappa and C kappa genes in hybrid clones retaining different human chromosomes indicated that C kappa is distal to V kappa on 2p and that the breakpoint in this Burkitt lymphoma is within the region carrying V kappa genes. High levels of transcripts of the c-myc gene were found when it resided on the 8q+ chromosome but not on the normal chromosome 8, demonstrating that translocation of a kappa locus to region distal to the c-myc oncogene enhances c-myc transcription.

38. CHROMOSOME TRANSLOCATIONS, IMMUNOGLOBULIN GENES, AND NEOPLASIA

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Cancer: Etiology and Prevention. Crispin RG, ed. New York, Elsevier Science Publishing Co., 463 pp., pp. 91-107, 1983.

Based on previously reported findings that genes for human Ig heavy chains, kappa light chain, and lambda light chain are located in the terminal portion of the long arm of chromosome 14, the short arm of chromosome 2 (2p), and the long arm of chromosome 22 (22q), respectively, that about 90% of the neoplastic cells of Burkitt lymphomas have a characteristic translocation involving the terminal portions of chromosomes 8q and 14q, that, in murine leukemias, chromosome translocations involving Ig gene segments may bring 'promoter' DNA sequences into juxtaposition with other DNA sequences and thereby activate the latter sequences to play a role in cellular transformation, and that in the avian myelocytomatosis system cell oncogenes may be activated by the insertion of viral 'promoter' DNA adjacent to the oncogenes, the possibility was considered that a promoter mechanism of translocations involving Ig genes might operate in lymphoid tumors. To test these concepts of human leukemogenesis, studies were undertaken using several Burkitt tumor cell lines and techniques of mouse-human cell hybridization. By this means it was demonstrated that the breakpoint on chromosome 14 in the Burkitt tumor involved the Ig heavy chain locus, with a portion of the locus translocated to chromosome 8; also, that the human analogue of the viral myelocytomatosis gene is located on the terminal portion of chromosome 8q and is translocated to chromosome 14, adjacent to Ig gene sequences in the tumor. These results were consistent with the hypothesis. (28 Refs)

39. TRANSCRIPTIONAL ACTIVATION OF THE TRANSLOCATED C-MYC ONCOGENE IN BURKITT LYMPHOMA

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Proc Natl Acad Sci USA; 80(3):820-824 1983

We have previously demonstrated that translocations of VH genes from chromosome 14 to chromosome 8 and of the c-myc oncogene from chromosome 8 to chromosome 14 occur in Burkitt lymphomas with the t(8;14) chromosome translocation. An association of the c-myc gene with the Cmu immunoglobulin gene has been observed in some but not all Burkitt lymphomas studied previously. In the present study, we have investigated the organization of the human heavy chain locus and of the c-myc gene in the P3HR-1 Burkitt lymphoma cell line. Because mouse/P3HR-1 somatic cell hybrids that retain only the 14q+ chromosome and no other human chromosomes contain the human Cmu and Cgamma genes but not VH genes, we have concluded that the breakpoint on chromosome 14 in P3HR-1 cells is distal to Cmu and between Cmu and VH. Thus, the breakpoint of human chromosome 14 differs in different Burkitt lymphoma cell lines. We also found that the human c-myc oncogene translocated to chromosome 14 in the P3HR-1 cell line is not recombined with the Cmu gene. The breakpoint on human chromosome 8 may therefore also differ in different Burkitt lymphoma cell lines, because we have observed DNA rearrangement of the c-myc gene with the Cmu gene in only some of the Burkitt lymphoma cell lines studied elsewhere. Interestingly, high levels of transcripts of the c-myc oncogene were observed in Burkitt lymphomas with translocated c-myc oncogenes both rearranged and unrearranged. Therefore, the translocation of a c-myc oncogene to the heavy chain locus on human chromosome 14 is apparently sufficient for its transcriptional activation and may be an essential step in the pathway leading to neoplasia. (Author abstract) (36 Refs)

40. IDENTIFICATION OF RECIPROCAL TRANSLOCATION SITES WITHIN THE C-MYC ONCOGENE AND IMMUNOGLOBULIN MU LOCUS IN A BURKITT LYMPHOMA

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Nature; 306(5945):799-803 1983

The association between certain human tumours and characteristic chromosomal abnormalities has led to the hypothesis that specific cellular oncogenes may be involved and consequently 'activated' in these genetic recombinations. This hypothesis has found strong support in the recent findings that some cellular homologues of retroviral onc genes are located in chromosomal segments which are affected by specific tumour-related abnormalities (see ref. 4 for review). In the case of human undifferentiated B-cell lymphoma (UBL) and mouse plasmacytomas, cytogenetic and chromosomal mapping data have identified characteristic chromosomal recombinations directly involving different immunoglobulin genes and the c-myc oncogene (for review see refs 5, 6). In UBLs carrying the t(8;14) translocation it has been shown that the human c-myc gene is located on the region of chromosome 8 (8q24) which is translocated to the immunoglobulin heavy-chain locus (IHC) on chromosome 14. Although it is known that the chromosomal breakpoints can be variably located within or outside the c-myc locus and within the IHC mu (refs 9, 11) or IHC gamma locus, the recombination sites have not been exactly identified and mapped in relation to the functional domains of these loci. We report here the

identification and characterization of two reciprocal recombination sites between c-myc and IHC mu in a Burkitt lymphoma. Nucleotide sequencing of the cross-over point joining chromosomes 8 and 14 on chromosome 14q shows that the onc gene is interrupted within its first intron and joined to the heavy-chain mu switch region. This recombination predicts that the translocated onc gene would code for a rearranged mRNA but a normal c-myc polypeptide.

41. TRANSCRIPTIONALLY ACTIVE C-MYC ONCOGENE IS CONTAINED WITHIN NIARD, A DNA SEQUENCE ASSOCIATED WITH CHROMOSOME TRANSLOCATIONS IN B-CELL NEOPLASIA

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Proc Natl Acad Sci USA; 80(2):519-523 1983

NIARD (non-immunoglobulin-associated rearranging DNA) is located on mouse chromosome 15 at the break point of a commonly observed translocation event involving chromosomes 15 and 12 in murine plasmacytomas. The human cellular analogue of the v-myc oncogene of avian myelocytomatosis virus, strain MC-29, is known to reside on the distal end of human chromosome 8 and has been observed to translocate to chromosome 14 in Burkitt lymphomas. Using a cDNA clone specific for the transcript of the human c-myc gene (H c-myc), we show that the mouse c-myc (M c-myc) gene is contained within NIARD. NIARD-associated chromosome translocations occurred 1.3-2 kilobases (kb) 5' of the mouse c-myc gene where NIARD recombines with the switch region of the Calpha immunoglobulin gene in various murine plasmacytomas. The mouse c-myc encoding region within NIARD spanned less than 2.4 kb of DNA and expressed a low level of a 2.3-kb polyadenylated RNA in BALB/c spleen. Increased (10- to 20-fold) levels of rearranged mouse c-myc transcripts (ie, approx 1.8-2.1 kb) were observed in plasmacytomas that have NIARD-associated chromosome translocations. Human c-myc and NIARD probes detected DNA rearrangements of human c-myc in four of seven Burkitt lymphomas. DNA sequences adjacent to the human c-myc gene recombined with the Cu immunoglobulin gene locus on chromosome 14 in several Burkitt lymphomas. The activation of the c-myc oncogene by chromosome translocation implicates its involvement in B-cell oncogenesis. (Author abstract) (27 Refs)

42. TRANSCRIPTIONAL ACTIVATION OF AN UNREARRANGED AND UNTRANSLOCATED C-MYC ONCOGENE BY TRANSLOCATION OF A C LAMBDA LOCUS IN BURKITT

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Proc Natl Acad Sci USA; 80(22):6922-6 1983

We have studied somatic cell hybrids between mouse myeloma cells and IARC-BL2 Burkitt lymphoma human cells carrying a t(8;22) chromosome translocation for the presence and expression of human immunoglobulin lambda chains and for the c-myc oncogene. The results indicate that the c-myc oncogene remains on the 8q+ chromosome and that the excluded and rearranged C lambda allele translocates from chromosome 22 to this chromosome 8. As a result of the translocation, transcriptional activation of the c-myc oncogene on the rearranged chromosome 8 (8q+) occurs, while the c-myc oncogene in the normal chromosome 8 is transcriptionally silent. These findings suggest that the translocation of a rearranged immunoglobulin locus to the 3' side of

an unrearranged c-myc oncogene may enhance its transcription and contribute to malignant transformation.

43. SYNTHESIS OF KAPPA LIGHT CHAINS BY CELL LINES CONTAINING AN 8;22 CHROMOSOMAL TRANSLOCATION DERIVED FROM A MALE HOMOSEXUAL WITH BURKITT'S LYMPHOMA

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Science; 222(4628):1094-8 1983

Three cell lines were derived from a homosexual patient with probable acquired immunodeficiency syndrome and Burkitt's lymphoma. The cell lines produce an unusual strain of Epstein-Barr virus which will both transform cord blood lymphocytes and induce early antigens in Raji cells. Translocations between chromosomes 8 and 22 have occurred in all three lines, but the cells synthesize immunoglobulin M with light chains of the kappa type, in contrast to the usual concordance between a translocation involving chromosome 22 and lambda chain synthesis. Both kappa genes and one lambda gene are rearranged. These findings indicate either that translocation may occur as a separate event from immunoglobulin gene rearrangement or that the proposed hierarchical sequence of immunoglobulin gene rearrangements is not always adhered to. The data also imply that in cells containing a translocation between the long arm of chromosome 8 and a chromosome bearing an immunoglobulin gene, alteration of cellular myc expression may occur regardless of the immunoglobulin gene that is expressed.

44. TRANSLOCATION JOINS C-MYC AND IMMUNOGLOBULIN GAMMA 1 GENES IN A BURKITT LYMPHOMA REVEALING A THIRD EXON IN THE C-MYC ONCOGENE

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Nature; 304(5922):135-9 1983

Recombinant DNA clones have been used to directly demonstrate that the Burkitt lymphoma cell line Raji, t(8;14)(q24;q32), has a rearranged copy of the c-myc gene adjacent to the gamma 1 constant region gene of the human immunoglobulin heavy-chain locus; the genes are arranged in the opposite direction for transcription. At least one further 5' exon has been detected in the normal c-myc gene by analysis of RNA transcripts, and the occurrence of high levels of two c-myc mRNA size classes, both apparently initiating in this exon, is described.

45. TRANSCRIPTION ENHANCER IDENTIFIED NEAR THE HUMAN C MU IMMUNOGLOBULIN HEAVY CHAIN GENE IS UNAVAILABLE TO THE TRANSLATED C-MYC GENE IN A BURKITT LYMPHOMA

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Nature; 306(5945):806-9 1983

In Burkitt lymphoma the c-myc gene, the cellular homologue of the viral oncogene v-myc, has been implicated in the aetiology of this human B-cell malignancy. Burkitt lymphoma cells possess specific chromosomal rearrangements involving the region proximal to the c-myc gene and one of the three human immunoglobulin loci. The nature of the effect exerted by the immunoglobulin loci on the translocated c-myc gene is controversial: whereas some reports have suggested c-myc transcription is elevated in Burkitt lymphoma cells, others have suggested the level of transcription is unaffected by the translation. Recently, transcription enhancer elements

have been identified in the intron between the JH and C mu segments of the heavy-chain immunoglobulin gene in mice. If similar enhancers exist in humans they may lead to increased transcription of the translocated c-myc gene and thus contribute to oncogenesis in Burkitt lymphoma. We report here the identification of an enhancer element adjacent to the human C mu gene on normal chromosome 14, but this enhancer does not remain on the abnormal chromosome 14 to which the c-myc gene has been translocated in the Burkitt lymphoma cell line Raji. This element is, therefore, not available for control of the translocated c-myc gene in this case.

46. THE HUMAN C-MYC ONCOGENE: STRUCTURAL CONSEQUENCES OF TRANSLOCATION INTO THE IGH LOCUS IN BURKITT LYMPHOMA

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Cell; 34(3):779-87 1983

We have determined the sequence of the normal human c-myc gene and compared it to portions of a c-myc gene that has been translocated into the immunoglobulin heavy chain locus in a Burkitt lymphoma cell. The normal c-myc gene is encoded in three discrete exons divided by two large intervening sequences. Its mRNA is transcribed from two active promoters located about 150 nucleotides from one another. Each promoter initiates transcription of a long (approximately 550 bp) untranslatable leader sequence encoding the entire first exon. This exon and additional 5' flanking sequences are tightly conserved between mouse and man. In the Burkitt cell BL22, the rearranged c-myc gene retains both promoters and is unchanged in its amino acid coding domains. Translocation of this gene joins it to the immunoglobulin heavy chain switch region at a point approximately 1000 bp 5' to the dual c-myc promoters. These genes are joined in opposite transcriptional orientation. The structure of the translocated gene and the nature of its linkage to the immunoglobulin locus and the presence of two c-myc promoters and consequently two long leader sequences raise novel possibilities for the activation of an oncogene.

47. EVIDENCE FOR INVOLVEMENT OF THE IMMUNOGLOBULIN HEAVY-CHAIN GENE LOCUS IN THE 8;14 TRANSLOCATION OF HUMAN B LYMPHOMAS

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Int J Cancer; 31(3):275-279 1983

The authors have re-examined their data on Ig synthesis in human lymphoid cell lines and expanded their analysis of those cell lines carrying an 8;14 translocation to determine its effect, if any, on heavy-chain expression. Abnormalities of immunoglobulin (Ig) heavy chain synthesis occurring in human B lymphoid cell lines of malignant origin suggest that the Ig heavy-chain gene complex is involved in the 8;14 chromosome translocation which these cells carry. (28 Refs)

48. ALTERED NUCLEOTIDE SEQUENCES OF A TRANSLOCATED C-MYC GENE IN BURKITT LYMPHOMA

Rabbitts TH, Hamlyn PH, Baer R
MRC Laboratory of Molecular Biology, Cambridge, UK.
Nature; 306(5945):760-5 1983

The nucleotide sequence of a translocated c-myc gene in a Burkitt lymphoma reveals multiple base changes in the

coding region. Twenty-five base changes, generating 16 codon alterations, were found in the first coding exon; no changes occur in the second coding exon. These changes are probably the result of somatic mutations that occurred during and after translocation, and may contribute to oncogenesis by allowing synthesis of an altered c-myc gene product.

49. SEQUENCE OF THE MURINE AND HUMAN CELLULAR MYC ONCOGENES AND TWO MODES OF MYC TRANSCRIPTION RESULTING FROM CHROMOSOME TRANSLOCATION IN B LYMPHOID TUMOURS

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EMBO J; 2(12):2375-83 1983

The 15;12 chromosome translocation in murine plasmacytomas and the 8;14 in human Burkitt lymphomas often link the cellular myc oncogene to the locus for constant regions of immunoglobulin heavy chains (CH locus). To clarify how and why c-myc translocation occurs, we have sequenced the mouse and human c-myc genes and correlated c-myc transcription with c-myc rearrangement. Both genes comprise three exons; the second and third encode the myc polypeptide, which is conserved between mammals and birds, particularly in its more basic C-terminal half. Southern blots showed that four of 12 Burkitt lines have c-myc linked near CH switch regions and two near the joining region (JH) locus. Hence, immunoglobulin recombination machinery may participate in translocation, although the common myc breakpoint region around exon 1 does not resemble a switch region. Tumours with breakpoints just 5' to exon 1, or distant from c-myc, had normal c-myc mRNAs of 2.25 and 2.4 kb, which differ at their 5' ends, while tumours with breakpoints within exon 1 or intron 1 had altered c-myc mRNAs (2.1-2.7 kb in Burkitt lines), initiated within intron 1. Both types of mRNAs probably yield the same polypeptide. Since the untranslocated c-myc allele was generally silent, translocation to the CH locus must induce constitutive c-myc expression. The presence of c-myc mRNA in immortal but non-tumorigenic lymphoblastoid cell lines may implicate c-myc in an immortalization step.

50. DIFFERENTIAL EXPRESSION OF THE TRANSLOCATED AND THE UNTRANSLOCATED C-MYC ONCOGENE IN BURKITT LYMPHOMA

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Science; 222(4622):390-3 1983

Burkitt lymphoma cells carrying either a rearranged or un-rearranged c-myc oncogene were examined with the use of probes from the 5' exon and for the second and third exon of the oncogene. The results indicate that the normal c-myc gene on chromosome 8 and the 5' noncoding and 3' coding segments of the c-myc oncogene separated by the chromosomal translocation are under different transcriptional control in the lymphoma cells. Burkitt lymphoma cells carrying a translocated but unrearranged c-myc oncogene express normal c-myc transcripts. In contrast, lymphoma cells carrying a c-myc gene rearranged head to head with the immunoglobulin constant mu region gene express c-myc transcripts lacking the normal untranslated leader.

51. DIFFERENTIAL EXPRESSION OF THE NORMAL AND OF THE TRANSLOCATED HUMAN C-MYC ONCOGENES IN B CELLS

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Proc Natl Acad Sci USA; 80(15):4822-6 1983

We have investigated whether the translocated and the untranslocated human c-myc oncogenes of Burkitt lymphoma cells are equally or differentially expressed in host mouse P₃ cells. The human c-myc mRNA levels in somatic cell hybrids between mouse plasmacytoma cells and Burkitt lymphoma cells with either the t(8;14) or the t(2;8) chromosome translocation were determined by using the nuclease S1 protection procedure. Although both the human parental lines and the hybrid cells carrying the translocated c-myc oncogene expressed high levels of human specific c-myc transcripts, the hybrid cells carrying the untranslocated c-myc gene on normal chromosome 8 did not contain human specific c-myc mRNA. These results suggest that the translocated human c-myc oncogene has escaped the normal transcriptional control to which the untranslocated c-myc gene remains subjected. This interpretation is also supported by the finding that the expression of the c-myc genes of lymphoblastoid cells and of HL-60 promyelocytic leukemia cells are repressed when they are transferred into a mouse plasmacytoma background. The ability of the translocated c-myc oncogene to escape the normal transcriptional control occurring in B cells may be important for the expression of B cell neoplasia in mouse and man. We have also transferred the Burkitt 14q+ chromosome carrying a translocated c-myc oncogene into mouse LM-TK- fibroblasts and studied the levels of human c-myc transcripts in the hybrids. Because the levels of human c-myc transcripts in the fibroblast hybrids are dramatically decreased in comparison to the plasmacytoma hybrids, we conclude that the levels of transcripts of the translocated c-myc oncogene depend on the differentiated state of the cells harboring the translocated chromosome.

52. EXPRESSION OF CELLULAR MYC AND MOS GENES IN UNDIFFERENTIATED B CELL LYMPHOMAS OF BURKITT AND NON-BURKITT TYPES

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Proc Natl Acad Sci USA; 80(7):1947-1950 1983

Burkitt lymphomas contain reciprocal translocations between chromosome 8 and one of the chromosomes containing the immunoglobulin gene loci, prompting speculation that consequent activation of a crucial gene(s) on chromosome 8 might be involved in the generation of these tumors. Recently the human counterparts of the retroviral oncogenes v-myc and v-mos have been mapped to chromosome 8. We have, therefore, analyzed the level of transcription of the cellular myc and mos genes in a variety of undifferentiated B cell lymphomas of Burkitt and non-Burkitt types that possess either an 8;14 or an 8;22 translocation. These lines expressed 2- to 5-fold more myc-specific RNA than do B cell lines without a translocation. Tumor cell lines of American origin with an 8;14 or 8;22 translocation expressed similar amounts of myc-specific RNA. Tumor cell lines of African origin contained slightly higher levels of myc-specific RNA than did those of American origin. However, level of expression does not appear to correlate with the presence or absence of Epstein-Barr virus. Therefore, a major increase in the transcription of this gene secondary to translocation is unlikely to be the cause of Burkitt's lymphoma. There was no evidence of mos

related transcripts in any of the cell lines tested. (Author abstract) (36 Refs)

53. HUMAN AND MOUSE CELLULAR MYC PROTOONCOGENES RESIDE ON CHROMOSOMES INVOLVED IN NUMERICAL AND STRUCTURAL ABERRATIONS IN CANCER

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Somatic Cell Genet; 9(3):391-405 1983

A molecular clone of viral myc (v-myc), the oncogene of avian myelocytomatosis virus, MC29, detected homologous human, mouse, and Chinese hamster cellular myc (c-myc) sequences by Southern filter hybridization. A v-myc probe, containing sequences from the 3' domain of the gene, hybridized to single human HindIII and mouse EcoRI genomic DNA fragments of the cellular myc genes whose segregation could be followed in interspecies somatic cell hybrids. Human c-myc segregated concordantly with the enzyme marker glutathione reductase and with a karyotypically normal chromosome 8. A rearrangement of human c-myc was observed in Burkitt's lymphoma cells possessing the t(8;14) translocation. These results suggest that human c-myc is located close to the breakpoint on chromosome 8 (q24) involved in the t(8;14) translocation. The mouse c-myc gene segregated concordantly with chromosome 15 in mouse-Chinese hamster cell hybrids. These gene assignments are noteworthy, as structural and numerical abnormalities of human chromosome 8 and mouse chromosome 15 are associated frequently with B-cell neoplasms.

54. TWO HUMAN C-ONC GENES ARE LOCATED ON THE LONG ARM OF CHROMOSOME 8

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Proc Natl Acad Sci USA; 79(24):7842-7846 1982

We have used in situ chromosome hybridization techniques to map the human cellular counterparts (c-onc genes) of the transforming genes of two RNA tumor viruses on human meiotic pachytene and somatic metaphase chromosomes. We find that the human c-mos gene is located on Chromosome 8 at a position corresponding to band 8q22 on the somatic map. The human c-myc gene is found on Chromosome 8 at position 8q24. These regions on the long arm of Chromosome 8 have been previously reported to be involved in specific translocations found in the M-2 subset of acute nonlymphoblastic leukemias, Burkitt lymphoma, and other forms of non-Hodgkin lymphoma, and a familial abnormality that predisposes to renal cell carcinoma. These results suggest that translocations of the human c-mos or c-myc genes may be causally related to neoplastic transformation. (Author abstract) (63 Refs)

55. TRANSLOCATION OF THE C-MYC GENE INTO THE IMMUNOGLOBULIN HEAVY CHAIN LOCUS IN HUMAN BURKITT LYMPHOMA AND MURINE PLASMACYTOMA CELLS

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Proc Natl Acad Sci USA; 79(24):7837-7841 1982

The consistent appearance of specific chromosomal translocations in human Burkitt lymphomas and murine plasmacytomas has suggested that these translocations might play a role in malignant transformation. Here we show that transformation of these cells is frequently accompanied by the somatic rearrangement of a cellular analogue of an avian retrovirus

transforming gene, c-myc. Moreover, we map c-myc to human Chromosome 8 band q24, the chromosomal segment involved in the reciprocal Burkitt translocation [t(8;14), t(8;22), and t(2;8)]. In two t(8;14) human Burkitt cell lines, c-myc appears to have been translocated directly into a DNA restriction fragment that also encodes the immunoglobulin mu chain gene. In the case of a specific cloned fragment of DNA derived from a mouse plasmacytoma, we demonstrate directly that c-myc has been translocated into the immunoglobulin alpha switch region. Our data provide a molecular basis for considering the role that specific translocations might play in malignant transformation. (Author abstract) (35 Refs)

56. HUMAN C-MYC ONC GENE IS LOCATED ON THE REGION OF CHROMOSOME 8 THAT IS TRANSLOCATED IN BURKITT LYMPHOMA CELLS

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Proc Natl Acad Sci USA; 79(24,Suppl):7824-7827 1982

Human sequences related to the transforming gene (v-myc) of avian myelocytomatosis virus (MC29) are represented by at least one gene and several related sequences that may represent pseudogenes. By using a DNA probe that is specific for the complete gene (c-myc), different somatic cell hybrids possessing varying numbers of human chromosomes were analyzed by the Southern blotting technique. The results indicate that the human c-myc gene is located on Chromosome 8. The analysis of hybrids between rodent cells and human Burkitt lymphoma cells, which carry a reciprocal translocation between Chromosomes 8 and 14, allowed the mapping of the human c-myc gene on region (q24 to qter) of Chromosome 8. This chromosomal region is translocated to either human Chromosome 2, 14, or 22 in Burkitt lymphoma cells. (Author abstract) (35 Refs)

57. TRANSLOCATION OF IMMUNOGLOBULIN VH GENES IN BURKITT LYMPHOMA

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Proc Natl Acad Sci USA; 79(10):5611-5615 1982

We have produced cell hybrids between mouse myeloma cells, which do not produce immunoglobulin chains, and Burkitt lymphoma cells (Daudi), which express surface IgM. Daudi cells carry a reciprocal chromosome translocation between chromosomes 8 and 14, described as t(8;14)(q24;q32). The hybrids were studied for the expression of human immunoglobulin chains and human isozyme markers, for the presence of human chromosomes, and for the presence of the human genes for heavy chain variable regions (VH) and mu and gamma chain constant (C) regions. The results indicate that the expressed mu chain gene is on normal chromosome 14 in Daudi cells. We have also determined that the chromosome 14 involved in the translocation (14q+) carries the gene for Cmu and Cgamma1-4 and probably several genes for the variable region (V). Certain hybrids had lost both the chromosomes 14 but had retained the abnormal chromosome 8 (8q-) that carries the terminal end of the long arm of chromosome 14. These hybrids were studied for the presence of human VH, Cmu, and Cgamma DNA sequences, and the results indicated that the hybrid cells with the 8q- chromosome contained VH genes but not C genes. Therefore, we conclude that, in the Daudi Burkitt lymphoma, the break in chromosome 14 occurred within the chromosome segment containing V region genes. As a result of the translocation some of these VH genes became

associated with chromosome 8. It is possible that the expression of malignancy in Burkitt lymphoma is caused by immunoglobulin V region gene translocation resulting in activation of a gene on the long arm of human chromosome 8. (Author abstract) (34 Refs)

2.

Myc Translocations in Murine Plasmacytomas

58. REGULATION OF TRANSLOCATED C-MYC GENES TRANSFECTED INTO PLASMACYTOMA CELLS

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Proc Natl Acad Sci USA; 83(3):706-9 1986

We have transfected two translocated c-myc oncogene clones, derived from two human lymphomas carrying the t(8;14) chromosome translocation, into mouse plasmacytoma cells to study the regulation of their expression. In one case, the transfected clone contained the two coding exons of the c-myc oncogene translocated to an immunoglobulin heavy-chain switch region; in the other case, the two coding exons were translocated 5' of the enhancer element located between the heavy-chain joining region (JH) and the switch region S mu. Nuclease S1 protection experiments indicate that only the c-myc translocated 5' of the enhancer element is transcribed in the plasmacytoma cells. Thus, 5'-truncation of the c-myc gene per se does not lead to c-myc deregulation. Further, since the level of c-myc transcripts in the parental human lymphoma cells was 3- to 4-fold higher than in the transfectants, it seems likely that additional elements within the heavy-chain locus may play a role in the enhancement of c-myc gene transcription in lymphoma cells.

59. METHYLATION OF PLASMACYTOMA C-MYC GENES

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Gene; 39(2-3):287-92 1985

The chromosomal translocation associated with many tumors of immunoglobulin-producing cells frequently results in the joining of the immunoglobulin heavy-chain locus and the c-myc oncogene. This translocation of c-myc has profound structural and functional consequences for the oncogene, including loss of the 5' end of the gene and transcriptional deregulation. We report in this communication that translocation results in a new methylation pattern of c-myc. In normal kidney and liver tissue, the c-myc gene is methylated at its 3' end. The translocated gene in plasmacytoma DNA is extensively demethylated. On the other hand, the nonrearranged c-myc gene in plasmacytoma DNA (which is transcriptionally silent) is extensively methylated. In addition, we confirm the nucleotide sequence (with 19 discrepancies out of 1400 bp) 5' to the murine c-myc gene, as reported by Corcoran et al. [Cell 40 (1983) 71-79].

60. CHROMATIN STRUCTURE OF THE MURINE C-MYC LOCUS: IMPLICATIONS FOR THE REGULATION OF NORMAL AND CHROMOSOMALLY TRANSLOCATED GENES

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EMBO J; 4(12):3195-202 1985

To assess possible alterations of c-myc transcriptional control in murine B-cell tumors, we have investigated the pattern of DNaseI hypersensitive sites in the gene's putative regulatory region and within the gene in a variety of genomic contexts. A number of such sites were found in several cell types, but none of these was detectable in a gene which was shown to

be transcriptionally silent by the criterion of elongation of nascent transcripts in isolated nuclei. These results differ from those of a previous study, in which a DNaseI-hypersensitive site approximately 2 kb upstream of the gene was proposed to be associated with negative regulation of c-myc transcription in human cells. An analysis of DNA sequences presented here reveals that this region is highly homologous between mouse and human, suggesting that these upstream hypersensitive sites do not reflect species-specific regulatory elements. We also present data indicating that this hypersensitive site distinguishes the c-myc alleles in translocation-positive plasma cell tumors which lack c-myc rearrangement. Furthermore, we report the existence of hypersensitive sites within the gene. One of these appears to be associated with cryptic promoters that are employed only when the normal promoters are lost as a consequence of chromosome translocation. These results are discussed in the context of c-myc translocation and gene breakage and with respect to possible stage-specific regulation of the gene's transcriptional competence.

61. MAPPING OF THE C-MYC, PVT-1 AND IMMUNOGLOBULIN KAPPA GENES IN RELATION TO THE MOUSE PLASMACYTOMA-ASSOCIATED VARIANT (6;15) TRANSLOCATION BREAKPOINT

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EMBO J; 4(12):3183-8 1985

A variant mouse plasmacytoma (MPC)-associated translocation chromosome has arisen by pericentric inversion and exchange of the distal segments of a Robertsonian 6;15 fusion chromosome in the CAK TEPC 1198 mouse plasmacytoma, as described earlier. In situ hybridization was performed on the normal and the inverted Rb chromosomes, using myc and kappa probes. On the normal Rb chromosome, myc was in the 15 D2/3 region, whereas kappa hybridized in the 6 C2 area, as expected. On the inverted Rb chromosome, myc remains on the centromeric side of the translocation breakpoint on the chromosome 15-derived portion, whereas kappa has moved to the chromosome 6-derived segment that joined the same breakpoint on the telomeric side. Taken together with our recent demonstration that the murine c-myc locus is oriented 'head up' on chromosome 15, and with the results of Cory and co-workers concerning the relationship between the kappa gene and the associated pvt-1 region in the CAK TEPC 1198 tumor, the following conclusions can be drawn: (i) in the variant translocation of the CAK TEPC 1198 MPC, the breakage occurs 3' of the c-myc gene, as in the human Burkitt lymphoma-associated variant translocations; (ii) the pvt-1 gene on chromosome 15 is distal to the myc gene; (iii) the kappa light chain locus is oriented 'head up' on mouse chromosome 6 and faces pvt-1 and, beyond it, c-myc, in a head-to-tail configuration.

62. TRANSPOSITION OF THE IMMUNOGLOBULIN HEAVY CHAIN ENHANCER TO THE MYC ONCOGENE IN A MURINE PLASMACYTOMA

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Cell; 40(1):71-9 1985

A novel mechanism of oncogene activation by transposition of a tissue-specific cellular enhancer is described. A rearranged c-myc oncogene was cloned from murine plasmacytoma ABPC17 in the expectation that it would reflect the t(6;15) chromosome translocation carried by this tumor. The

rearrangement instead reflects an insertion 361 bp 5' to the c-myc gene on chromosome 15. The insert conveys a 2.3 kb segment of the immunoglobulin heavy (H) chain locus from chromosome 12. Since the insertion introduces the lymphoid-specific enhancer from the JH-Smu region and also disrupts a region implicated in normal c-myc control, it may account for the c-myc transcription observed in ABPC17. The structure of the transposed segment and a corresponding deletion in the JH-Smu region suggests that the transposition reflects a complex recombination between chromosomes 15 and 12. Since the t(6;15) breakpoint is not near c-myc, chromosome 15 must have undergone an independent exchange with chromosome 6.

63. CHROMOSOME TRANSLOCATION ACTIVATES HETEROGENEOUSLY INITIATED, BIPOLAR TRANSCRIPTION OF A MOUSE C-MYC GENE

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EMBO J; 4(3):667-74 1985

In many mouse plasmacytomas, the active c-myc gene has been truncated by chromosome translocation with the resultant severance of the protein-coding sequence from the normal promoter. Transcripts of such truncated c-myc genes were analyzed by Northern blotting, nuclease S1 mapping, primer extension assays and cDNA cloning. We conclude that transcription originates from multiple initiation sites on both c-myc coding and non-coding strands with the two-sets of transcripts derived from adjacent but essentially non-overlapping regions located greater than 1 kb from the translocation junction. In X63Ag8, where c-myc is translocated to the immunoglobulin C gamma 2b gene, the c-myc non-coding strand transcripts include the translocation junction and then splice directly into the gamma 2b CH1 exon. We propose that chromosome translocation activates a cryptic promoter in the first intron and that the heterogeneously initiated, bipolar transcription reflects the absence of a suitably placed TATA box element.

64. POSTTRANSCRIPTIONAL MECHANISMS ARE RESPONSIBLE FOR ACCUMULATION OF TRUNCATED C-MYC RNAs IN MURINE PLASMA CELL TUMORS

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Cell; 42(2):589-97 1985

c-myc Messenger RNAs are known to be extremely unstable ($t_{1/2} = 10$ min) in normal and tumor cells, suggesting that degradation could play an important role in regulating their steady state level in the cytoplasm. We have investigated the stabilities of c-myc mRNAs in three murine plasmacytomas, where the c-myc gene either remains intact (ABPC20) or exists in a truncated form (MPC-11 and J558L) subsequent to 6;15 or 12;15 chromosome translocations respectively, and in an A-MuLV-induced pre-B lymphoma line (18-81.5) that lacks chromosome translocations and contains both c-myc genes in their normal context. The truncated myc genes in J558L and MPC-11 lack the promoters of the normal gene but are transcribed from cryptic promoters within the first c-myc intron. We found that posttranscriptional processes are largely responsible for the higher steady state accumulations of truncated c-myc transcripts, while broken and intact c-myc genes are transcribed at comparable rates.

65. CHROMOSOME TRANSLOCATIONS CLUSTERED 5' OF THE MURINE C-MYC GENE QUALITATIVELY AFFECT PROMOTER USAGE: IMPLICATIONS FOR THE SITE OF NORMAL C-MYC REGULATION

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EMBO J; 4(6):1441-7 1985

Five novel murine plasma cell (PC) tumors with chromosome translocations 350-500 bp 5' of the first c-myc exon are described. The t(12;15)s of TEPC 1194, ABPC 33 and TEPC 1165 position the intact c-myc locus 5' of the C α , C gamma 2a and C alpha IgCH genes respectively. In ABPC 17, the IgH enhancer element and adjacent switch (Su) sequences were found 5' of the first c-myc exon while this enhancer is associated with the reciprocal products of the TEPC 1194, ABPC 33 and TEPC 1033 translocations. Quantitative S1 nuclease analyses demonstrate that the ratios of transcription from the two c-myc promoters (P1 and P2) are increased 4-to 7-fold in these five tumors. With the exception of TEPC 1165, (which contains a small deletion in exon 1), such increases in P1:P2 ratios appear to be manifested by a reduction in P2 usage in comparison to other tumors without such promoter shifts. A survey of 27 additional PC and non-PC B lymphoid tumors and cell lines revealed that myc promoter shifts of this magnitude are unique to PC tumors with 5'-proximal translocations. We propose that (i) these clustered breakpoints identify a normal c-myc regulatory element located at least 350 bp 5' of c-myc exon 1; (ii) the loss or disruption of this cis-acting upstream element and the linkage of c-myc to the IgCH locus would result in abnormal expression of this oncogene in these as well as most other PC tumors.

66. VARIANT (6;15) TRANSLOCATIONS IN MURINE PLASMACYTOMAS INVOLVE A CHROMOSOME 15 LOCUS AT LEAST 72 KB FROM THE C-MYC ONCOGENE

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EMBO J; 4(3):675-81 1985

The variant (6;15) translocations in murine plasmacytomas join the myc oncogene-bearing band of chromosome 15 and the immunoglobulin kappa band of chromosome 6. We recently cloned a region from chromosome 15 linked to C kappa and have now used probes from that region to define the major locus of plasmacytoma variant translocations, which we denote pvt-1. In five of nine plasmacytomas we analysed, the 6;15 translocation resulted from reciprocal recombination between the C kappa locus and a 4.5-kb region of pvt-1. Moreover, nearby we located the region shown by others to have undergone a complex (15;12;6) translocation in plasmacytoma PC7183. All the chromosome 6 breakpoints fell between 1 and 3 kb 5' to C kappa but only two were near J kappa genes. Thus the J kappa -C kappa region appears to be a recombination 'hot spot' in lymphocytes, but the breaks are unlikely to be mediated via V/J recombination enzymes. Comparison of a cloned 108-kb region across pvt-1 and another of 52 kb across c-myc established that the pvt-1 breakpoints lie at least 72 kb from the c-myc promoters. Since c-myc is expressed at a substantial level, the 6;15 translocation apparently activates c-myc. Activation may occur directly, at a remarkable distance along the chromosome, or indirectly, via a putative pvt-1 gene product.

67. THE C-MYC ONCOGENE IS TRANSLOCATED TO THE INVOLVED CHROMOSOME 12 IN MOUSE PLASMACYTOMA

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Proc Natl Acad Sci USA; 82(12):4212-6 1985

Although it is known that the c-myc oncogene is rearranged in a head-to-head fashion with the immunoglobulin heavy chain locus in mouse plasmacytomas, it has not been clear whether the c-myc oncogene is translocated to the heavy chain locus on mouse chromosome 12 or whether the heavy chain locus is translocated to the c-myc locus on mouse chromosome 15. To determine which of these two possibilities is correct, we hybridized Chinese hamster fibroblasts with J558 mouse plasmacytoma cells that carry a reciprocal chromosome translocation between chromosomes 12 and 15, and we examined the segregating hybrids for the presence of the normal and rearranged mouse c-myc genes, for the presence of different regions of the mouse heavy chain locus, and for the presence of genes located on mouse chromosomes 12 and 15. The results of this analysis indicate that, as in human Burkitt lymphomas with the 8;14 chromosome translocation, the c-myc gene is translocated to the heavy chain locus in mouse plasmacytomas. Thus the orientation of the heavy chain locus on mouse chromosome 12 and of the c-myc gene on mouse chromosome 15 is the same as the orientation of the homologous loci in man.

68. GENE LOCALIZATION ON SORTED CHROMOSOMES: DEFINITIVE EVIDENCE ON THE RELATIVE POSITIONING OF GENES PARTICIPATING IN THE MOUSE PLASMACYTOMA-ASSOCIATED TYPICAL TRANSLOCATION

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Proc Natl Acad Sci USA; 82(20):6975-9 1985

Experiments have been carried out to establish the relative position of the mouse Ig heavy chain locus and the c-myc oncogene. In mouse plasmacytoma with the typical rcpt(12;15) chromosome translocation the c-myc oncogene is juxtaposed to one of the heavy chain genes in a head-to-head orientation. Since the relative orientations of the c-myc locus and the Ig heavy chain gene cluster on the corresponding mouse chromosomes had not been settled, it was not known whether the rearranged c-myc gene is transposed to chromosome 12 or remains on chromosome 15. To decide which of the two alternatives is correct, we separated the translocation chromosomes by fluorescence-activated chromosome sorting. The separated chromosomal fractions were hybridized with myc-specific DNA probes corresponding to the first or second/third exons in a chromosome spot assay. The results presented here indicate that the c-myc gene in mouse plasmacytoma carrying the typical translocation, as in the human Burkitt lymphoma analogous translocation, transposes to the chromosome carrying the Ig heavy chain locus. These results also establish the orientations of the Ig heavy chain locus and the c-myc locus on their normal chromosomes.

69. CHROMOSOME TRANSLOCATIONS AND THE ACTIVATION OF C-MYC ONCOGENE IN MOUSE PLASMACYTOMAS

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Gan To Kagaku Ryobo; 11(3 Pt 2):587-96 1984

Plasmacytomas can be induced in BALB/c mice by three different agents: (1) Mineral oil, (2) Solid plastics such as diffu-

sion chambers, and (3) Abelson murine leukemia virus plus pristane. We examined chromosome aberrations in mouse plasmacytomas induced by each of the three agents. Most of plasmacytomas showed the specific translocations of chromosomes between either No. 12 and No. 15 or No. 6 and No. 13. These chromosome translocations were common to all plasmacytomas induced by different agents. The specific breakpoints were at 12F2 where IgH genes appear to locate, and 6C2 where kappa light chain genes might be located, and 15D2/3 where c-myc oncogene appears to locate. However, we have found very recently a few plasmacytomas which have no translocations of chromosomes. The subregion(s) of one copy of chromosome 15 which is called D1:D2 appears to be deleted in these plasmacytomas. In the next study, we examined the relationship of chromosomal aberrations to the activation of c-myc oncogene. Not only the plasmacytomas with chromosome translocations, but also the translocation-negative plasmacytomas showed either the rearrangement or germline type of c-myc DNA. Rearranged c-myc transcript was found only in plasmacytomas with the 12;15 translocation. However, not all plasmacytomas belonging to this group expressed the altered c-myc RNA transcript. Our experiments indicated that the germline type c-myc RNA was 2.4 kb and the rearranged c-myc RNA was mostly 1.8 kb in length. Concerning the c-myc DNA, the germline type was 21 kb and the rearranged type of c-myc DNA was estimated, mostly, to be 14 kb by EcoRI digestion.

70. ACTIVATION OF THE C-MYC ONCOGENE BY THE IMMUNOGLOBULIN HEAVY-CHAIN GENE ENHANCER AFTER MULTIPLE SWITCH REGION-MEDIATED CHROMOSOME REARRANGEMENTS IN A MURINE PLASMACYTOMA

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Proc Natl Acad Sci USA; 82(11):3746-50 1985

Presented is a detailed molecular analysis of the rearranged c-myc oncogene from ABPC45, an unusual plasmacytoma that was originally classified as translocation-negative. Previous data obtained by high-resolution chromosome banding suggested that this tumor was a member of a small group distinguished by the absence of rcpt(12;15) or (6;15) and further characterized by a band deletion near the c-myc locus on chromosome 15. However, genomic Southern blotting and analysis of the cloned oncogene in the present study reveal that (i) chromosome 12 sequences lie 365 base pairs 5' of the rearranged c-myc; (ii) this DNA consists of immunoglobulin alpha switch region and 5' immunoglobulin mu switch region sequences that are rearranged in an aberrant fashion; and (iii) the immunoglobulin heavy-chain gene enhancer element now resides approximately 2.5 kilobase pairs 5' of c-myc. We infer from these and other data that the rearrangement of c-myc in ABPC45 occurred via a multistep switch region-mediated process and that a reciprocal translocation has indeed taken place. Unlike many other plasmacytomas, this event did not interrupt the normal c-myc transcription unit. Rather, disruption of gene regulation is manifested in part by a change in relative usage of the two promoters normally used by the unrearranged gene. In contrast to several of its counterparts in Burkitt lymphomas, DNA sequence analysis of the translocated c-myc gene of ABPC45 reveals that it has not acquired point mutations in the non-coding first exon. These results strongly imply that a cis-acting regulatory element normally located 5' of exon 1 is lost and that heavy-chain constant region or enhancer sequences exert similar cis effects on translocated c-myc loci.

71. TRANSLOCATION OF THE MYC CELLULAR ONCOGENE TO THE IMMUNOGLOBULIN HEAVY CHAIN LOCUS IN MURINE PLASMACYTOMAS IS AN IMPRECISE RECIPROCAL EXCHANGE

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Cell; 36(4):973-82 1984

The 15;12 translocations in murine plasmacytomas represent recombination of the myc oncogene with the immunoglobulin CH locus, often within CH switch recombination (SH) regions. Chromosome junctions cloned from four plasmacytomas confirmed that the translocation generates reciprocal CHSH-myc and 5'myc-SH structures. H locus targets included S alpha fused to Smu, Smu fused to S gamma 2b, and a germline S alpha region. The nature of two H locus targets suggests that the target need not be highly active transcriptionally. Switch recombination machinery is implicated in the translocation by the SH targets and by homology of certain c-myc breakpoints with normal switch recombination sites. Fusion regions revealed deletions, extraneous nucleotides, and one duplication. These results prompt a translocation model in which staggered single-stranded breaks on each chromosome are followed by single-strand excision or polymerization prior to ligation to the other chromosome.

72. PRODUCTS OF A RECIPROCAL CHROMOSOME TRANSLOCATION INVOLVING THE C-MYC GENE IN A MURINE PLASMACYTOMA

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Proc Natl Acad Sci USA; 81(3):829-33 1984

The structures of the rearranged c-myc gene products derived from a reciprocal T(12;15) have been investigated in the MPC-11 (IgG2b kappa) plasmacytoma. The reciprocal T(12;15) in MPC-11 is a reciprocal exchange between the c-myc gene on chromosome 15 and the immunoglobulin gamma 2a switch region (S gamma 2a) on chromosome 12. The c-myc gene is broken within a 5'-nontranslated exon, thereby separating the promoter region of the normal c-myc gene from its protein coding sequences. This reciprocal rearrangement results in the loss of 11 base pairs of c-myc sequence and 300 base pairs of S gamma 2a sequence at the point of recombination. Sequences that represent the promoter region of the normal c-myc gene are present in the 5'-myc reciprocal fragment. A comparison of the nucleotide sequences at the recombination site of a number of c-myc rearrangements reveals a common feature that may have mechanistic importance for these translocation events.

73. TRANSCRIPTIONAL ACTIVATION OF THE TRANSLOCATED C-MYC ONCOGENE IN MOUSE PLASMACYTOMAS: SIMILAR RNA LEVELS IN TUMOR AND PROLIFERATING NORMAL CELLS

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Cell; 37(2):521-8 1984

We examine the influence of the immunoglobulin locus on the expression of the translocated c-myc oncogene in mouse plasmacytomas. The level of c-myc RNA was 30-35-fold greater in tumor cells than in normal, quiescent B cells. Mitogen stimulation of the lymphocytes with lipopolysaccharide induced a 15-fold increase in c-myc expression per cell to a level that was similar to that in the transcription of the translocated c-myc gene involved initiation from sequences in the first c-myc intron. Abundant RNA transcripts were also

found from the noncoding strand of the c-myc intron in most tumor lines. S1 nuclease mapping was used to locate the intronic sequences that are used to initiate the tumor-specific c-myc RNAs. Six different initiation sites within the intron were mapped, none of which have the TATA sequence usually associated with eucaryotic RNA polymerase II promoters. The noncoding strand transcripts were also found to initiate in the c-myc intron. Transcription of the c-myc coding strand was independent of the position of the translocation breakpoint, even when the heavy chain switch and constant regions were deleted.

74. VARIANT (6; 15) TRANSLOCATION IN A MURINE PLASMACYTOMA OCCURS NEAR AN IMMUNOGLOBULIN KAPPA GENE BUT FAR FROM THE MYC ONCOGENE

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Nature; 312(5996):777-9 1984

Chromosome translocations in B-lymphoid tumours are providing intriguing insights and puzzles regarding the role of immunoglobulin genes in the activation of the myc oncogene (reviewed in refs 1, 2). The 15; 12 translocations found in most murine plasmacytomas and the analogous 8; 14 translocation in human Burkitt's lymphomas involve scissions of murine chromosome 15 (human chromosome 8) near the 5' end of the c-myc gene and subsequent fusion near an immunoglobulin heavy-chain gene. The less well characterized 'variant' translocations found in about 15% of such tumours also involve the myc-bearing chromosome band, but exchange occurs with a chromosome bearing an immunoglobulin light-chain locus - in mice, the kappa-chain locus bearing chromosome 6 (refs 3-5) and, in man, chromosome 2 (or 22), at the same band at which the kappa (or lambda) locus lies (reviewed in ref. 1). The Burkitt variant translocations involve scissions 3' of c-myc; one 8; 22 translocation placed the C lambda locus just 3' of c-myc, but usually the chromosome 8 breakpoint is a greater, but unknown, distance away from c-myc, more than 20 kilobases (kb) in one 8; 2 translocation involving the C kappa gene. Little is known about the murine 6; 15 translocations, although a C kappa gene cloned from one plasmacytoma (PC7183) is linked, via chromosome 12 sequences, to an unidentified region of chromosome 15 (ref. 11). We describe here the chromosome fusion region from plasmacytoma ABPC4, which displays the typical reciprocal 6;15 translocations. We find that the chromosome 6 breakpoint is near C kappa but, unlike those in the heavy-chain locus, not at a position where immunoglobulin genes normally recombine. Moreover, the chromosome 15 sequences involved in the ABPC4 translocation are not derived from the vicinity of c-myc.

75. A NOVEL 6;10 CHROMOSOMAL TRANSLOCATION IN THE MURINE PLASMACYTOMA NS-1

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Nature; 307(5950):473-6 1984

Specific chromosomal abnormalities are regularly associated with many murine and human malignancies. In particular, the majority of murine plasmacytomas and human Burkitt's lymphomas contain a characteristic translocation which results in the juxtaposition of a cellular oncogene, c-myc, with the immunoglobulin heavy-chain gene locus, and this rearranged c-myc directs the synthesis of qualitatively and quantitatively abnormal transcripts which may have an aetiological role in the development of the transformed state in lymphoid malignancies. Similarly, rearrangement and abnormal ex-

pression of c-myc (ref. 10) and c-mos (ref. 11) has been reported in other murine lymphoid tumours. Here we describe a novel 6:10 chromosomal translocation in the murine plasmacytoma cell line NS-1 which juxtaposes the immunoglobulin C κ gene with a single-copy sequence of unknown function. The NS-1 plasmacytoma is a frequently used fusion partner in hybridoma production and is known to contain a rearranged c-myc gene and a genetic element which transforms normal mouse fibroblasts in DNA-mediated transfection assays. We conclude that individual B-cell tumours may contain multiple chromosomal translocations perhaps relevant to oncogenesis.

76. TRANSLOCATION AFFECTS NORMAL C-MYC PROMOTER USAGE AND ACTIVATES FIFTEEN CRYPTIC C-MYC TRANSCRIPTION STARTS IN PLASMACYTOMA M603

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Nucleic Acids Res; 12(23):8987-9007 1984

Plasmacytoma M603 contains one normal, nontranslocated c-myc gene and one translocated c-myc gene in which c-myc exon 1 is juxtaposed with the immunoglobulin heavy chain enhancer and c-myc exons 2 and 3 are juxtaposed with C α . We find that steady-state c-myc RNA levels are 2-4 fold elevated in M603 relative to normal liver or spleen and that these transcripts originate predominantly if not exclusively from the translocated c-myc gene. Although both promoters on the nontranslocated c-myc gene are repressed, the proximal promoter, P1, is active on the translocated 5' c-myc region which is juxtaposed with the immunoglobulin heavy chain enhancer. The 3' portion of the translocated c-myc gene is transcribed from fifteen cryptic start sites and spliced at aberrant donor and acceptor splice sites, thereby generating a mixture of transcripts with different, abnormal 5' untranslated regions. Although the reason that translocation activates the cryptic c-myc starts in M603 is not completely understood, we show that truncation of the c-myc gene is not sufficient to activate cryptic transcription sites.

77. A CONSERVED SEQUENCE AT C-MYC ONCOGENE CHROMOSOMAL TRANSLOCATION BREAKPOINTS IN PLASMACYTOMAS

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Nature; 310(5975):327-30 1984

Many recent studies have shown that chromosomal translocation breakpoints frequently occur near cellular proto-oncogenes (reviewed in ref. 1). In both mouse plasmacytomas and Burkitt lymphomas, the c-myc oncogene becomes joined to an immunoglobulin heavy-chain gene in a head-to-head configuration. Within c-myc, the breaks frequently occur near the first exon-intron boundary, while within the immunoglobulin gene the breaks usually involve sequences directing heavy-chain switching. It has been assumed that the translocations represent abortive immunoglobulin switching events which have activated the c-myc gene for a role in tumour formation. However, sequence analysis of the c-myc gene does not reveal any apparent similarity to the immunoglobulin switch signals. With these results in mind, we have determined the precise breakpoints within c-myc for two plasmacytoma lines in order to search for any common features that may shed some light on the mechanism of chromosomal translocation. We report here that the tetranucleotide sequence GAGG occurs close to the breakpoint in five out of six translocations, and so may be a sequence recognized

by either the enzymes that catalyse immunoglobulin heavy-chain switching, or some other DNA-cleaving activity.

78. NUCLEOTIDE SEQUENCE COMPARISON OF NORMAL AND TRANSLOCATED MURINE C-MYC GENES

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Nature; 310(5976):423-5 1984

Plasmacytoid tumours in mice and Burkitt's lymphomas in humans display characteristic chromosomal translocations involving the c-myc proto-oncogene. Models to explain quantitative changes in c-myc expression have been proposed based on the loss of normal promoters as a result of translocation. However, alternative explanations, such as somatic mutation are needed to explain altered c-myc expression in the absence of gene breakage. We present here the nucleotide sequence of the normal murine c-myc gene. Comparison of this sequence with that of a translocated c-myc gene from a murine plasmacytoma reveals complete identity of coding sequence. One nucleotide difference was found in the non-coding first exon. This shows that qualitative changes of the c-myc gene product are not required for oncogenesis in murine plasmacytomas. In contrast, mutations are found in coding and non-coding regions of translocated c-myc genes from Burkitt's lymphomas, suggesting that the mechanisms by which c-myc is activated in plasmacytomas and Burkitt's lymphomas are different.

79. HIGH RESOLUTION BANDING ANALYSIS OF THE INVOLVEMENT OF STRAIN BALB/C- AND AKR-DERIVED CHROMOSOMES NO. 15 IN PLASMACYTOMA-SPECIFIC TRANSLOCATIONS

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J Exp Med; 159(1):276-91 1984

Plasmacytomas were induced in (BALB/c X AKR 6;15) X BALB/c backcross mice where one of the BALB/c-derived chromosomes No. 15 was replaced by the AKR(6;15)-derived Robertsonian 6;15 chromosome. (BALB/c X AKR 6;15)F₂ mice that were homozygous for Rb 6;15 were mated to BALB/c mice. Plasmacytomas were induced in the progeny by intraperitoneal injection of pristane. The cytogenetic marker permitted the distinctive identification of the two chromosome 15 homologues, including the distal segment involved in the plasmacytoma-specific translocations. 7 of the 10 plasmacytomas contained the typical t(12;15) translocation. The BALB/c-derived 15 chromosome served as the donor of the translocated segment in six of them. In the seventh, the Rb 6;15 chromosome of the AKR strain was the donor. The remaining three tumors contained the same type of intrachromosomal rearrangement. It arose by the pericentric inversion of the Rb 6;15 chromosome, leading to a variant plasmacytoma-associated rcpt (6;15) translocation. Unlike the usual 6;15 variant that arises by a reciprocal exchange between two separate chromosomes, it was generated by an exchange of the distal segments of a single chromosomal element. High resolution banding analysis of the tumors showed that all translocated breakpoints on chromosomes 15, 12, and 6 were identical with the previously described breakpoints characteristic for the typical 12;15 and the variant 6;15 translocation in murine plasmacytomas. It is known that the distal segment of chromosome 15 carries the c-myc oncogene (23). The PC-associated translocations cut across the 5'-exon of c-myc in the majority of the cases (24,26). The severed oncogene is transposed to the Ig-region on the recipient chromosome. Since

the BALB/c strain is highly sensitive to PC-induction, we were interested to examine the question whether its chromosome 15 is preferred as the oncogene donor in AKR X BALB/c backcross mice that carry cytogenetically distinguishable 15 chromosomes. Our results show that this is not the case, since the same segment of the AKR-derived chromosome 15 could also serve in the same capacity. This is in contrast with T cell leukemogenesis where we have previously found that the trisomization-associated duplication of chromosome 15 occurred in a highly asymmetrical fashion, depending on the donor strain of No. 15 (9-11).

80. MODES OF C-MYC ONCOGENE ACTIVATION IN MURINE PLASMACYTOMAS

Yang JQ, Musbinski JF, Stanton LW, Fahrlander PD, Tesser PC, Marcu KB

Curr Top Microbiol Immunol; 113:146-53 1984

Keywords (MeSH): Animal; Base Sequence; Cell Line; Cell Transformation, Neoplastic; Chromosome Aberrations; Mice; *Oncogenes; Operon; Plasmacytoma/*familial and genetic; Translocation (Genetics).

81. DNA SEQUENCES INVOLVED IN THE REARRANGEMENT AND EXPRESSION OF THE MURINE C-MYC GENE

Dunnick W, Baumgartner J, Fradkin L, Schultz C

Curr Top Microbiol Immunol; 113:154-60 1984

Keywords (MeSH): Animal; Base Sequence; Cell Line; Cell Transformation, Neoplastic; Comparative Study; DNA/isolation and purification; DNA, Neoplasm/*genetics/isolation and purification; Human; Kidney/analysis; Liver/analysis; Methylation; Mice; Mice, Inbred BALB C; *Oncogenes; Plasmacytoma/*familial and genetic; Species Specificity; Transcription, Genetic; Translocation (Genetics).

82. TRANSCRIPTIONAL ACTIVATION OF IMMUNOGLOBULIN ALPHA HEAVY-CHAIN GENES BY TRANSLOCATION OF THE C-MYC ONCOGENE

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Nature; 305(5933):443-6 1983

Our previous studies with the mouse myeloma MOPC 315 (IgA, lambda 2) cell line, using myeloma mutants that had deleted the productive alpha heavy (H)-chain gene, had shown that the excluded alpha constant-region (C alpha) allele in these cells is transcriptionally active. Recent reports from several laboratories have demonstrated that in many BALB/c mouse myelomas, including MOPC 315, the DNA segment encoding the c-myc oncogene is translocated to a C alpha allele. The mRNA coding strand of DNA for the c-myc gene is on the opposite strand from the immunoglobulin gene in this locus. We have now investigated the relationship between the c-myc translocation and transcriptional activity of excluded C alpha alleles in IgA- and IgG-producing mouse myeloma lines. We report here that c-myc-C alpha recombination events correlate with demethylation and transcription of C alpha genes. Several novel C alpha RNA species are produced, which are transcribed from the immunoglobulin-gene sense strand. The larger C alpha RNAs appear to contain c-myc sequences. Thus the anti-sense strand of the c-myc gene provides a promoter for transcription of the C alpha gene. This result suggests that in other transformed cells with a c-myc-immunoglobulin gene translocation, including many Burkitt's lymphomas, activation of the adjacent immunoglobulin gene would occur.

83. INTERCHROMOSOMAL RECOMBINATION OF THE CELLULAR ONCOGENE C-MYC WITH THE IMMUNOGLOBULIN HEAVY CHAIN LOCUS IN MURINE PLASMACYTOMAS IS A RECIPROCAL EXCHANGE

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EMBO J; 2(5):697-703 1983

The 15:12 chromosome translocations found in most murine plasmacytomas involve the cellular gene (c-myc) homologous to the oncogene (v-myc) of avian retrovirus MC29. Translocation links the c-myc gene of chromosome 15 to the immunoglobulin heavy (H) chain locus of chromosome 12, often within the switch recombination (S) region 5' to the alpha constant region (C alpha) gene. We have investigated c-myc rearrangements in 21 BALB/c plasmacytomas and three B lymphomas by Southern blot analysis. We show that the t(15;12) is a reciprocal chromosome exchange since most tumours contain not only a c-myc gene linked to the S alpha C alpha region but also a separate structure with S mu or S alpha linked to the c-myc 5'-flanking region. Analysis of the two rearrangement products cloned from plasmacytoma J558 suggests that one type of H locus target for translocation is an S alpha region recombined with S mu; two other targets appear to be other switched heavy chain genes and an un-rearranged C alpha gene. Nearly all the chromosome 15 breakpoints fall within a 1.1-kb region spanning a 5' c-myc exon; hence scission of the transcriptional unit by translocation can account for the altered c-myc transcription in plasmacytomas. The c-myc breakpoint region lacks substantial homology with S mu or S alpha, arguing against homologous recombination as the translocation mechanism.

84. TRANSLOCATION, BREAKAGE AND TRUNCATED TRANSCRIPTS OF C-MYC ONCOGENE IN MURINE PLASMACYTOMAS

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Nature; 303(5916):401-6 1983

Comparative nucleotide sequence analysis of a rearranged c-myc gene in a murine plasmacytoma and c-myc cDNA from normal spleen reveals that chromosomal translocation in the plasmacytoma breaks the c-myc gene within the first exon or intron. In the plasmacytoma truncated c-myc RNAs initiate from newly exposed promoter sites. Nevertheless, the myc polypeptide produced in the plasmacytoma is probably the same as that from the intact c-myc gene because the exon lost by breakage and translocation is non-coding. The second and third exons of the mouse c-myc gene are substantially conserved in the v-myc gene of the avian retrovirus, MC29.

85. CELLULAR MYC ONCOGENE IS ALTERED BY CHROMOSOME TRANSLOCATION TO AN IMMUNOGLOBULIN LOCUS IN MURINE PLASMACYTOMAS AND IS REARRANGED SIMILARLY IN HUMAN BURKITT LYMPHOMAS

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Proc Natl Acad Sci USA; 80(7):1982-1986 1983

Molecular cloning has recently established that the 15:12 chromosome translocations in murine plasma cytomas fuse DNA from chromosome 15 to the immunoglobulin heavy (H) chain locus, usually within the switch recombination region near the alpha constant region gene. We show here that the incoming DNA bears the cellular gene (c-myc) homologous to the oncogene (v-myc) of avian retrovirus MC29.

In human Burkitt lymphomas bearing an 8;14 translocation, c-myc was also rearranged, apparently (in at least 2 cases) to an H chain switch recombination region (μ or α), and both products of a reciprocal chromosome exchange were detectable. Both the murine and human c-myc genes contain two exons homologous to v-myc, and additional 5' and 3' murine genomic segments (apparent exons) were defined by hybridization to c-myc mRNAs. In plasmacytomas, chromosome breakpoints fall near or within the 5' exon and apparently disrupt the normal c-myc transcriptional unit, because plasmacytoma c-myc mRNAs differ from the mRNA in lines without c-myc rearrangement. The translocated gene presumably has lost its normal 5' regulatory sequences and may well encode an altered myc polypeptide. We propose that altered expression of the c-myc gene, induced by translocation to an immunoglobulin locus, is a critical oncogenic event for these B lymphoid tumors. Two events may be required, because the plasmacytoma oncogene capable of transforming fibroblasts is not c-myc. (Author abstract) (41 Refs)

86. DNA SEQUENCES NEAR THE SITE OF RECIPROCAL RECOMBINATION BETWEEN A C-MYC ONCOGENE AND AN IMMUNOGLOBULIN SWITCH REGION

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Proc Natl Acad Sci USA; 80(23):7269-73 1983

The chromosomal translocations found in many B-cell tumors result in the joining of a c-myc oncogene with an immunoglobulin heavy chain switch region. This finding is striking because the natural function of switch regions is to mediate DNA rearrangements important to the maturation of immune responses. These normal switch rearrangements are probably mediated by specific enzymes. In this paper we report the isolation of the two reciprocal products of a recombination between a c-myc gene on murine chromosome 15 and an immunoglobulin switch region (S μ S gamma 2b) on chromosome 12. We have determined the sequences of these DNA molecules near the recombination sites and show that the recombination is nearly perfectly reciprocal, with a seven-nucleotide deletion. An examination of the sequences reported in this paper, and of sequences published by other authors, shows a correlation between the points of recombination for c-myc-S segment rearrangements and for normal heavy chain switches. We suggest that this correlation implies a role for switch recombination enzymes in creating substrates for the c-myc recombination. The c-myc gene also seems to share some limited homology to sequences thought to be important in heavy chain switching. Finally, we discuss a working model that accounts for some characteristics of c-myc-S segment recombinations. The model also suggests a mechanism for increased transcriptional activity of the rearranged c-myc oncogene in B-cell tumors.

87. RECIPROCAL CHROMOSOME TRANSLOCATION BETWEEN C-MYC AND IMMUNOGLOBULIN GAMMA 2B GENES

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Nature; 305(5931):240-3 1983

Specific chromosome translocations have been observed in transformed cell lines of both man and mouse and may be implicated in the origin or maintenance of malignancy. In mouse plasmacytomas, translocations have been identified that bring the immunoglobulin alpha heavy-chain gene (C alpha, normally located on chromosome 12) into proximity with c-myc (normally located on chromosome 15), c-myc being the mouse cellular homologue of the avian myelocytomatosis virus transforming gene (v-myc). Here we identify a

DNA rearrangement in a mouse hybridoma that has brought c-myc close to C gamma 2b and show that this rearrangement occurred by reciprocal chromosome translocation, as recombinant clones were isolated from the same cell line in which a rearranged variable-region (VH) gene has been brought close to 5' c-myc sequences. The translocation has resulted in the net loss of 7 base pairs (bp) of chromosome 15 sequence as well as in the presence of an additional base of unknown provenance. This reciprocal translocation was analysed in DNA from a mouse hybridoma cell line but is shown to be characteristic of the X63Ag8 myeloma parent.

88. RAT C-MYC ONCOGENE IS LOCATED ON CHROMOSOME 7 AND REARRANGES IN IMMUNOCYTOMAS WITH T(6;7) CHROMOSOMAL TRANSLOCATION

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Nature; 306(5942):497-8 1983

Two B-cell-derived tumours, human Burkitt's lymphoma (BL) and murine plasmacytoma (MPC), are regularly associated with a distinctive form of chromosomal translocation (for reviews see refs 1, 2). In BL, the distal portion of chromosome 8 breaks off and is transposed, in most cases, to chromosome 14, known to carry the immunoglobulin heavy-chain locus. In about 5% of the cases the same distal part of the chromosome 8 has moved to either chromosome 2 or 22, to the neighbourhood of the kappa or the lambda locus, respectively. In MPC the distal region of chromosome 15 is transposed to the chromosome 12, known to carry the immunoglobulin heavy-chain locus, or enters into reciprocal exchange with the kappa locus-carrying chromosome 6 (ref. 7). Several laboratories have located c-myc, the cellular homologue of the MC29 retroviral oncogene v-myc, to human chromosome 8 (refs 8-10) and mouse chromosome 15 (refs 11-13). It has also been shown that the BL- and MPC-associated translocations remove the c-myc gene from its original site and transpose it into or close to one of the immunoglobulin gene clusters. In view of the above findings we also looked for possible involvement of the c-myc gene in a B-cell-derived tumour of a third species, the rat. Rat immunocytomas of spontaneous origin carry a reciprocal translocation between chromosomes 6 and 7 (ref. 17). Here we have localized the c-myc locus to chromosome 7 of the rat. Moreover, we have found that the c-myc gene was rearranged in four of five immunocytomas carrying the characteristic chromosomal translocation.

89. MOUSE C-MYC ONCOGENE IS LOCATED ON CHROMOSOME 15 AND TRANSLOCATED TO CHROMOSOME 12 IN PLASMACYTOMAS

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Science; 218(4579):1319-1321 1982

DNA from a murine plasmacytoma clone (alpha30) containing a translocation of the distal part of chromosome 15 to chromosome 12 or 6 was hybridized with the following viral oncogenes: feline sarcoma virus, Y73 avian sarcoma virus, MC29, avian myelocytomatosis virus (v-myc probe), Abelson leukemia virus, avian erythroblastosis virus, SR-A avian sarcoma virus, and avian myeloblastosis virus. The v-myc probe hybridized to alpha30 sequences, but the others did not, suggesting that the mouse homologue of cellular myelocytomatosis (c-myc) oncogene is present on alpha30. The region of alpha 30 hybridizing with the v-myc probe was a 2.7-kilobase (kb) sequence bounded on one side by a Hind III site and on the other by an Xba I site. This region is lo-

cated about 1 kb from the junction of chromosome 15 and chromosome 12 on alpha30. The 5' and 3' orientation of mouse c-myc sequences was determined by probing Sst I digests of alpha30 with 5' and 3' fragments from the v-myc probe generated by restricting the cloned DNA with Sal I. The 3' fragment of v-myc hybridized to both Sst I fragments, while the 5' fragments of v-myc hybridized only to the 1.5 kb Sst I fragment, indicating that the orientation of the c-myc sequences in alpha30 is opposite to that of the immunoglobulin Calpha gene. Additional experiments demonstrated that a gene other than the translocated c-myc gene is translocated in murine plasmacytoma and causes the transformation of NIH-3T3 cells in transfection experiments. (14 Refs)

90. NOVEL MYC ONCOGENE RNA FROM ABORTIVE IMMUNOGLOBULIN-GENE RECOMBINATION IN MOUSE PLASMACYTOMAS

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Cell; 31(2,part1):443-452 1982

We have found that the myc oncogene has been modified by abortive recombination with the alpha heavy-chain immunoglobulin constant-region (Calpha) gene in five different mouse plasmacytoma lines. Recombination occurred approx 0.8-2.0 kb to the 5' side of two distinct coding regions, defined by sequence homology between the chicken cellular and plasmacytoma myc genes. The myc and Calpha genes were always in opposite transcriptional orientation, with the recombination site within the Calpha switch region sequences. DNA recombination was found to correlate with the production of a novel 2.1 kb species of myc RNA that was 0.4 kb shorter than the normal cellular transcript. No elevated levels of myc RNA were evident, suggesting that DNA rearrangements have altered the myc oncogene product. This oncogene activation corresponds to the chromosomal translocations found in nearly all plasmacytomas. (Author abstract) (52 Refs)

3.

Myc Translocations Occurring in Other Lymphomas, Leukemias, and Neoplastic Cells

91. REARRANGEMENT AND ENHANCED EXPRESSION OF C-MYC ONCOGENE IN FRESH TUMOR CELLS OBTAINED FROM A PATIENT WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Leuk Res; 10(4):381-7 1986

Both enhanced and altered expressions of cellular oncogenes have recently been implicated in specific forms of human malignancy (for review: [2, 8]). The fact that certain human tumors have characteristic chromosomal translocations has led to the hypothesis that specific cellular oncogenes may be 'activated' in these genetic recombinations. In a number of human undifferentiated B-cell lymphoma (UBL) cell lines carrying the t(8;14) translocation it has been shown that the human c-myc gene is located on the region of chromosome 8 (8q24), which is translocated to the immunoglobulin heavy-chain (IHC) locus on chromosome 14 [7, 24]. We report here the molecular cloning of the recombination site between c-myc and IHC in fresh uncultured cells obtained from a patient with rapidly progressive and fatal acute lymphoblastic leukemia. The translocation was associated with an enhanced c-myc expression in the tumor cells of this patient.

92. MYC ONCOGENE ACTIVATION IN B AND T LYMPHOID TUMOURS

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Proc R Soc Lond Biol; 226(1242):59-72 1985

The chromosome translocations characteristic of certain B lymphoid tumours associate the myc oncogene and immunoglobulin loci. The typical t(12;15) in murine plasmacytomas and analogous t(14;8) in Burkitt lymphomas couple the myc coding region to one of the switch recombination regions within the immunoglobulin heavy (H) chain locus; hence the switch machinery may promote some translocations. Significantly, translocation induces constitutive myc expression, the untranslocated myc allele remaining silent. The predilection for breakpoints near the 5' end of the c-myc gene may reflect selection for altered myc regulation. In most tumours, the stimulatory effect of the H locus context is not understood, but an H locus enhancer participates in some tumours, including one displaying a novel transposition. The variant t(6;15) translocations found in about 15% of plasmacytomas involve the myc band and the region of chromosome 6 where the kappa locus lies. The t(6;15) is shown here to represent an exchange between C kappa and a chromosome 15 locus (designated pvt-1) which lies unexpectedly far from c-myc. The association of myc expression with pvt-1 alterations suggest that myc can be activated at a distance. Myc has also been implicated in some T lymphomas by detection of proviral inserts near myc and also, surprisingly, within the pvt-1 locus. Inserts near myc appear to activate its expression via the retroviral enhancer.

93. TRANSLOCATION OF C-MYC IN THE HEREDITARY RENAL CELL CARCINOMA ASSOCIATED WITH A T(3;8)(P14.2;Q24.13) CHROMOSOMAL TRANSLOCATION

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Proc Natl Acad Sci USA; 82(20):6980-4 1985

A translocation between chromosomes 3 and 8, t(3;8)(p14.2;q24.13), has been reported in a family with hereditary renal cell carcinoma. Using somatic cell hybrids, we have isolated, separately, both derivative chromosomes. We find that the c-myc oncogene (8q24.1) has been translocated to the derivative 3 [der(3)]. We have not detected a rearrangement within an approximately equal to 21-kilobase region around the c-myc gene using restriction enzyme digestion and Southern blot hybridization analysis. The translocated c-myc gene should provide a probe to the chromosome 3p14 region, which appears to be important not only in renal cell carcinoma but also in small cell carcinoma of the lung. These hybrids have also been useful for the regional mapping of the Chinese hamster ovary cell Gly-B defect to 8q22.1 - - q24.13 and support the regional assignment of acylase I to 3p21.

94. REARRANGEMENT OF THE C-MYC PROTO-ONCOGENE LOCUS IN A CELL LINE OF T-LYMPHOBLASTIC ORIGIN

Caubet JF, Mathieu-Mabul D, Bernheim A, Larsen CJ, Berger R
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d'Hématologie, Hôpital Saint-Louis, Paris.
C R Acad Sci III; 300(5):171-6 1985

A molecular rearrangement of the proto-oncogene c-myc located downstream of the exon III 3' end has been found in a cell line derived from KE37 cell line established from an acute T-lymphoblastic leukemia. This rearrangement resulted from a chromosomal translocation t(8; 14)(q24; q11). Since

the 14q11 chromosomal band has been found to be involved in several T-cell leukemias and lymphomas, the importance of the rearrangement of c-myc discovered in the KE37 cell line lies in the possibility of analyzing chromosome 14 DNA near the breakpoint involved in the translocation.

95. REARRANGEMENT AND ACTIVATION OF THE C-MYC GENE IN AVIAN AND HUMAN B-CELL LYMPHOMAS (38 Refs)

Wiman KG, Hayward WS
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Tumour Biol; 5(5):211-9 1984

Keywords (MeSH): Animal; Avian Leukosis/*familial and genetic; B Lymphocytes; Base Sequence; Cell Transformation, Neoplastic; Cell Transformation, Viral; Gene Expression Regulation; Human; Lymphoma/*familial and genetic; Mutation; *Oncogenes; Review; RNA, Messenger/genetics; Transcription, Genetic; Translocation (Genetics).

96. ACTIVATION OF A TRANSLOCATED HUMAN C-MYC GENE BY AN ENHANCER IN THE IMMUNOGLOBULIN HEAVY-CHAIN LOCUS

Hayday AC, Gillies SD, Saito H, Wood C, Wiman K, Hayward WS, Tonegawa S
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Nature; 307(5949):334-40 1984

A tissue-specific transcriptional enhancer element that is associated with the human immunoglobulin heavy-chain locus is defined. In a non-Hodgkin's lymphoma that contains a translocated c-myc gene this enhancer is retained on the 14q+ chromosome and occurs within sequences shown to activate previously cryptic promoters of the c-myc gene.

97. REARRANGEMENT AND ABNORMAL EXPRESSION OF HUMAN C-MYC IN ACUTE LYMPHOCYTIC LEUKEMIA

Pesicble C, Mavilio F, Sposi NM, Giampaolo A, Care A, Bottero L, Bruno M, Mastroberardino G, Gastaldi R, Testa MG, et al
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Genetic and Phenotypic Markers of Tumors. Aaronson SA, Frati L, Verna R, eds. New York: Plenum Press, p. 311-21, 1984.

A case of acute lymphocytic leukemia (ALL), L3 type, with 8;14 chromosome translocation, whereby the c-myc is rearranged into the IgH locus, is reported. Two different c-myc transcripts were detectable at high levels in primary leukemic cells. Both virtually disappeared in the remission phase. These data extend and enhance the significance of the translocation-mediated c-myc activation in the genesis of B-cell neoplasias. The breakpoint of the translocation has been localized within the first intron of the c-myc gene, thus leaving the first untranslated exon on chromosome 8q- and rearranging the whole protein-coding region in the IgH locus on chromosome 14q+. Northern blot analysis revealed high levels of two different c-myc transcripts originated from the translocated gene; these high levels were not detected in WBC in remission phase. For the first time, rearrangement and abnormal expression of a cellular onc gene (c-myc) was demonstrated in primary cells from an ALL patient. (20 Refs)

98. TRANSLOCATION AND REARRANGEMENT OF C-MYC INTO IMMUNOGLOBULIN ALPHA HEAVY CHAIN LOCUS IN PRIMARY CELLS FROM ACUTE LYMPHOCYTIC LEUKEMIA

Pesicble C, Mavilio F, Sposi NM, Giampaolo A, Care A, Bottero L, Bruno M, Mastroberardino G, Gastaldi R, Testa MG, et al
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Proc Natl Acad Sci USA; 81(17):5314-8 1984

We report the molecular analysis of an 8;14 reciprocal chromosome translocation in a case of acute lymphocytic leukemia (L3 type). DNA from primary leukemic cells was ana-

lyzed on the basis of restriction endonuclease mapping by hybridization with various human c-myc and Ig heavy chain probes. The breakpoint of the translocation is within an approximately equal to 200-base-pair region in the first intron of the c-myc gene. The first, untranslated exon thereby remains on chromosome 8q-, whereas the whole protein-coding region is rearranged in the C alpha 1 locus on chromosome 14q+. RNA transfer blot analysis showed high levels of at least two different c-myc transcripts originated from the translocated gene. Both differ in size from the normal 2.2- and 2.4-kilobase transcripts. Both c-myc structure and expression were apparently normalized in remission phase. These studies demonstrate rearrangement and abnormal expression of c-myc in primary cells from an acute leukemia patient, thus adding to the concept of a key role for c-onc in human oncogenesis.

99. TRANSDUCTION AND REARRANGEMENT OF THE MYC GENE BY FELINE LEUKAEMIA VIRUS IN NATURALLY OCCURRING T-CELL LEUKAEMIAS

Neil JC, Hughes D, McFarlane R, Wilkie NM, Onions DE, Lees G, Jarrett O
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Nature; 308(5962):814-20 1984

Evidence of myc gene transduction by feline leukaemia virus in several spontaneous lymphoid tumours of cats suggests that recombinant viruses carrying oncogenes may be much more involved in oncogenesis in natural conditions than previously recognized.

100. CHANGES IN GENE POSITION ARE ACCOMPANIED BY A CHANGE IN TIME OF REPLICATION

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Cell; 36(3):689-96 1984

The globin and immunoglobulin multigene families have been used to study the effect of chromosomal organization on the time of gene replication. Some of the genes are late-replicating, providing the first identification of late-replicating sequences that are not highly repetitive. One is a member of the mouse alpha-globin gene family, which consists of genes mapping to three different chromosomes. The other genes in this family replicate early during S. Our studies demonstrate that immunoglobulin gene rearrangements and rearrangements between these genes and the c-myc oncogene are accompanied by dramatic differences in their temporal order of replication. We conclude that a gene's position in the chromosome, rather than its sequence, determines the time of replication. We suggest that the differences in association with gene rearrangement result from changes in the proximity of the affected gene to sites that control the temporal order of replication during S.

101. BIOLOGICAL ACTIVITIES OF V-MYC AND REARRANGED C-MYC ONCOGENES IN RAT FIBROBLAST CELLS IN CULTURE

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Proc Natl Acad Sci USA; 81(18):5758-62 1984

Two distinct forms of the myc oncogene were assayed for their ability to induce, in cultured rat fibroblast cells, the alterations of cellular growth controls observed upon transfer of the gene of polyoma virus encoding only the large T protein (plt). Both of these rearranged myc genes and the plt

gene had been previously shown to cooperate with ras oncogenes for transformation of rat embryo fibroblasts (REF) and were thought to induce the same early step ('immortalization') of the tumoral transformation pathway. We now report that these two different oncogenes elicit the same response in the following biological assays: (i) reduction of the requirements in serum factors for growth in culture of cells of the established FR3T3 line; (ii) expression of transformed properties in low serum medium after transfer into FR3T3 cells expressing only the middle T protein of polyoma virus (MTT lines); (iii) conferring on REF cells the ability to grow as clonal colonies after seeding at low cell density; (iv) conferring on REF cells the ability to grow continuously in cell culture. These congruent phenotypes suggest that the activities of the large T and myc proteins result in the induction of the same molecular events. These results also provide simple biological assays and selective systems for oncogenes of the myc class.

102. TRANSLOCATION AND REARRANGEMENTS OF THE C-MYC ONCOGENE LOCUS IN HUMAN UNDIFFERENTIATED B-CELL LYMPHOMAS

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New York, NY, 10016
Science; 219(4587):963-967 1983

The possibility was explored that the locus for the cellular myc (c-myc) oncogene in humans is altered as a consequence of chromosomal translocation in cells from patients with B-cell lymphoma. In humans the c-myc locus is located on the region of chromosome 8 that is translocated to chromosome 14 in cells from most undifferentiated B-cell lymphomas. In the studies reported, the c-myc locus was rearranged in 5/15 cell lines from patients with undifferentiated B-cell lymphomas; the rearrangement involved a region at the 5' side of an apparently intact c-myc gene. In one-third of the cell lines extensive sequence substitution at the 5' end of the c-myc gene was detected which otherwise appeared to be intact; these cases were all Epstein-Barr virus negative. By identifying two known genetic loci from different chromosomes involved in the translocation, it was possible to map, in three cell lines, the rearranged c-myc allele and variable parts of of the ICHmu locus in juxtaposition and thus locate the cross-over point between chromosomes 8 and 14. The break point can occur at different positions on both chromosomes among individual cell lines. (42 Refs)

103. ACTIVATION OF THE C-MYC GENE BY TRANSLOCATION: A MODEL FOR TRANSLATIONAL CONTROL

Saito H, Hayday AC, Wiman K, Hayward WS, Tomogawa S
Center for Cancer Research, Massachusetts Institute of Technology,
Cambridge.
Proc Natl Acad Sci USA; 80(24):7476-80 1983

We have shown that the human cellular oncogene c-myc is composed of three exons and is transcribed from two initiation sites separated by 175-base-pair DNA in HeLa cells. For both resulting mRNA species, exon 1 composes the 5' untranslated region and the initiator methionine is located 16 base pairs down-stream from the 5' splice acceptor of exon 2. In a non-Hodgkin lymphoma, Manca, harboring a t(8;14) translocation, c-myc gene is broken within intron 1, and its exons 2 and 3 are translocated to a site between the heavy chain joining region cluster and C mu-coding DNA segment of the immunoglobulin heavy chain locus. The translocated c-myc gene is transcribed from points within intron 1 but is apparently still translated from the same methionine codon as the mRNA from the unrearranged c-myc gene. The nucleotide sequence of the c-myc gene shows that a region of exon

1 is highly complementary to a region of exon 2. Thus the mRNA from the untranslocated c-myc gene, as opposed to that of the translocated c-myc gene, could form a stable stem-loop structure ($\Delta G_0 = -90$ kcal/mol; 1 cal = 4.184 J) where the initiator AUG would be located within the loop. In view of the bind-and-scan model for the initiation of eukaryotic translation, we propose that such a secondary structure will severely hinder the translation. We further propose that the c-myc gene is often activated by translocation through the escape from such a translational suppression.

104. NUCLEOTIDE SEQUENCE OF CLONED CDNA OF HUMAN C-MYC ONCOGENE

Watt F, Stanton LW, Marcu KB, Gallo RC, Croce CM, Rovera G
Wistar Institute of Anatomy and Biology, Philadelphia,
Pennsylvania.
Nature; 303(5919):725-8 1983

Like other transforming genes of retroviruses, the v-myc gene of the avian virus, MC29, has a homologue in the genome of normal eukaryotic cells. The human cellular homologue, c-myc, located on human chromosome 8, region q24 leads to qter (refs 1, 2), is translocated into the immunoglobulin heavy-chain locus on human chromosome 14 (ref. 3) in Burkitt's lymphoma, suggesting that c-myc has a primary role in transformation of some human haematopoietic cells. In addition, c-myc is amplified in the human promyelocytic leukaemia cell line, HL60 (refs 6, 7) which also contains high levels of c-myc mRNA. Recently, Colby et al. reported the nucleotide sequence of the human c-myc DNA isolated from a genomic recombinant DNA library derived from human fetal liver. This 4,053-base pair (bp) sequence includes two exons and one intron of the myc gene, and the authors have suggested the existence of a human c-myc mRNA of 2,291 nucleotides that has a coding capacity for a protein of molecular weight (Mr) 48,812. We have approached the problem of accurately defining the characteristics of the human c-myc mRNA and c-myc protein by determining the sequence of the c-myc cDNA isolated from a cDNA library prepared from mRNA of a clone of the K562 human leukaemic cell line. K562 cells are known to contain c-myc mRNA which is similar in size to the c-myc mRNA of other human cell types. We report here the sequence of 2,121 nucleotides of a human c-myc mRNA and demonstrate that its 5' noncoding sequence does not correspond to the sequence of the reported genomic human sequence. However, our data confirm that the intact human c-myc mRNA can encode a 48,812-Mr protein with a sequence identical to that reported by Colby et al.

4.

Reviews of Myc Translocations

105. ONCOGENES IN RETROVIRUSES, MALIGNANCY, AND NORMAL TISSUES

Lacey SW
University of Alabama, Birmingham.
Am J Med Sci; 291(1):39-46 1986

Oncogenes are genes with a proven cancer association that appear to function primarily in the regulation of cellular proliferation and differentiation. The preliminary work leading to their discovery, their association with retroviruses, the retrovirus life cycle, and the use of retroviruses to find and characterize oncogenes is discussed in detail. Chromosomal abnormalities are discussed using Burkitt's lymphoma and the myc oncogene as prototypes. Finally, the normal (nonmalignant) functioning of oncogenes is discussed in terms of embryogenesis and hepatic regeneration. (23 Refs)

106. DEREGULATION OF IMMUNOGLOBULIN EXPRESSION: IS THIS THE MAIN CAUSE OF BURKITT'S LYMPHOMA?

Morpurgo G

Dipartimento di Biologia Vegetale-Università degli Studi di Roma, La Sapienza, Italy.

J Theor Biol; 116(3):395-8 1985

We here examine the role of c-myc in the aetiology of Burkitt's lymphomas. We suggest that c-myc causes cellular clones to become immortal while the deregulation of cell multiplication is the consequence of an altered production and/or structure of immunoglobulin chains caused by the 8-14, 8-2 or 8-22 translocations. Data relative to other immunoproliferative disorders are consistent with the hypothesis that the immunoglobulins play a key role in the regulation of the multiplication of lymphocytic cells.

107. TRANSLOCATIONS AMONG ANTIBODY GENES IN HUMAN CANCER

Leder P

Department of Genetics, Harvard Medical School, Boston, MA.

IARC Sci Publ; (60):341-57 1985

The characteristic chromosomal translocations that occur in certain human malignancies offer opportunities to understand how two gene systems can affect one another when they are accidentally juxtaposed. In the case of Burkitt's lymphoma, such a translocation joins the cellular oncogene, c-myc, to a region encoding one of the immunoglobulin genes. In at least one example, the coding sequence of the rearranged c-myc gene is identical to that of the normal gene, implying that the gene must be quantitatively, rather than qualitatively, altered in its expression if it is to play a role in transformation. One might expect to find the rearranged c-myc gene in a configuration that would allow it to take advantage of one of the known immunoglobulin promoters or enhancer elements. However, the rearranged c-myc gene is often placed so that it can utilize neither of these structures. Since the level of c-myc messenger RNA is often elevated in Burkitt cells, the translocation may lead to a deregulation of the c-myc gene. Further, since the normal allele in a Burkitt cell is often transcriptionally silent in the presence of a rearranged allele, a model for c-myc regulation is suggested that involves a trans-acting negative control element that might use as its target a highly conserved portion of the c-myc gene encoding two discrete transcriptional promoters.

108. THE ROLE OF C-MYC IN THE PROLIFERATION OF NORMAL AND NEOPLASTIC CELLS (50 Refs)

Kelly K, Siebenlist U

Immunology Branch, National Cancer Institute, Bethesda, Maryland 20205.

J Clin Immunol; 5(2):65-77 1985

Keywords (MeSH): Animal; Burkitt's Lymphoma/familial and genetic/*pathology; Cell Cycle; *Cell Division; Cell Transformation, Neoplastic; Cell Transformation, Viral; Gene Expression Regulation; Growth Substances/physiology; Human; *Oncogenes; Review; Transcription, Genetic; Translocation (Genetics).

109. THE STATE OF AND PROSPECTS FOR MOLECULAR GENETICS IN BURKITT'S LYMPHOMA

Leder P

IARC Sci Publ; (60):475-6 1985

Keywords (MeSH): Burkitt's Lymphoma/diagnosis/*familial and genetic/therapy; Chromosomes, Human, 13-15; Chromosomes, Human, 6-12; Human; Oncogenes; Translocation (Genetics).

110. EVOLUTION OF TUMOURS AND THE IMPACT OF MOLECULAR ONCOLOGY

Klein G, Klein E

Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.

Nature; 315(6016):190-5 1985

It is generally accepted that tumours arise through the accumulation of several changes affecting the control of cell growth. Recent advances in molecular biology have made it possible to define some of these changes in molecular terms and to trace the steps by which certain tumours evolve. (146 Refs)

111. CHROMOSOMAL TRANSLOCATIONS, IMMUNOGLOBULIN GENES, AND ONCOGENES IN HUMAN B-CELL TUMORS

Nowell PC, Erikson J, Finan J, Emanuel B, Croce CM

Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia.

Prog Clin Biol Res; 184:457-68 1985

Keywords (MeSH): B Lymphocytes/*physiology; Burkitt's Lymphoma/*familial and genetic; Chromosomes, Human, 1-3; Chromosomes, Human, 13-15; Chromosomes, Human, 16-18; Chromosomes, Human, 21-22; Chromosome mes, Human, 6-12; Gene Expression Regulation; Human; Immunoglobulins, Heavy Chain/*genetics; Immunoglobulins, Light Chain/*genetics; Leukemia, Lymphocytic/familial and genetic; *Oncogenes; *Translocation (Genetics).

112. CHROMOSOMAL TRANSLOCATIONS, ONCOGENES, AND B-CELL TUMORS

Croce CM

Wistar Institute of Anatomy and Biology, Philadelphia.

Hosp Pract kOfit; 20(1):41-8 1985

Keywords (MeSH): Animal; B Lymphocytes; *Chromosome Aberrations; Human; Immunoglobulins, Lambda Chain/genetics; Lymphoma/*familial and genetic; *Oncogenes; *Translocation (Genetics).

113. FURTHER IMPLICATIONS OF THE TERRITORIAL EFFECTS OF GENES: CHROMOSOMAL TRANSLOCATION AND ONCOGENE ACTIVATION

Naora H, Miyabara K, Brasibwaite AW

Molecular Biology Unit, Research School of Biological Sciences, Australian National University, Canberra ACT.

J Theor Biol; 116(2):313-20 1985

Keywords (MeSH): Animal; Base Sequence; Burkitt's Lymphoma/familial and genetic; DNA/genetics; *Genes; Human; Mice; Models, Genetic; *Oncogenes; Plasmacytoma/familial and genetic; RNA, Messenger; Suppression, Genetic; Transcription, Genetic; *Translocation (Genetics).

114. GENE REGULATION IN THE EXPRESSION OF MALIGNANCY (38 Refs)

Croce CM

Monogr Pathol; (26):190-9 1985

Keywords (MeSH): Animal; B Lymphocytes/physiology; Burkitt's Lymphoma/familial and genetic; Cell Differentiation; Cell Transformation, Viral; Gene Expression Regulation; Human; Hybrid Cells/physiology; Neoplasms/*familial and genetic; *Oncogenes; Review; Translocation (Genetics).

115. CHROMOSOME ALTERATIONS IN ONCOGENESIS

Nowell PC, Emanuel BS, Finan JB, Erikson J, Croce CM

Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia.

Hematol Bluttransfus; 29:253-60 1985

Keywords (MeSH): Burkitt's Lymphoma/*familial and genetic; Cell Line; *Chromosome Aberrations; *Chromosome

Abnormalities; Gene Amplification; Human; Karyotyping; Leukemia/*familial and genetic; Leukemia, Myeloblastic; Lymphoma/*familial and genetic; *Oncogenes; Translocation (Genetics).

116. CHROMOSOMAL MECHANISMS IN NEOPLASIA (37 Refs)

de la Chapelle A

Department of Medical Genetics, University of Helsinki, Finland.
Prog Clin Biol Res; 177:139-52 1985

Keywords (MeSH): Burkitt's Lymphoma/familial and genetic; Cell Transformation, Neoplastic; *Chromosome Aberrations; Chromosome Banding; Chromosome Mapping; Chromosomes, Human, 21-22; Human; Karyotyping; Leukemia/*familial and genetic; Leukemia, Myeloblastic/familial and genetic; Leukemia, Myelocytic/familial and genetic; Neoplasms/*familial and genetic; Oncogenes; Review; Translocation (Genetics).

117. CHROMOSOME TRANSLOCATIONS AND HUMAN CANCER

Croce CM, Klein G

Sci Am; 252(3):54-60 1985

Keywords (MeSH): Animal; Antibody Formation; Burkitt's Lymphoma/familial and genetic; *Chromosome Aberrations; Chromosomes, Human, 13-15; Chromosomes, Human, 6-12; DNA/genetics; Human; Hybrid Cells/metabolism; Mice; Neoplasms/*familial and genetic/immunology; Oncogenes; Plasmacytoma/familial and genetic; *Translocation (Genetics).

118. MOLECULAR BASIS OF HUMAN B CELL NEOPLASIA (37 Refs)

Croce CM, Nowell PC

Wistar Institute of Anatomy and Biology, Philadelphia, PA.
Blood; 65(1):1-7 1985

Keywords (MeSH): Adult; Animal; B Lymphocytes/immunology/*pathology; Burkitt's Lymphoma/*familial and genetic/immunology; Cell Differentiation; Gene Expression Regulation; Genes, Structural; Human; Hybrid Cells/pathology; Immunoglobulins/genetics; Mice; Myeloblastosis Virus, Avian/genetics; Oncogenes; Review; *Translocation (Genetics).

119. ONCOGENE EXPRESSION IN BURKITT'S LYMPHOMA (34 Refs)

Nowell PC, Finan J, Erikson J, Croce CM

Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia, Pa.
Surv Synth Pathol Res; 3(4):350-7 1984

Keywords (MeSH): Animal; Burkitt's Lymphoma/familial and genetic/*immunology; C-Type Viruses/genetics; Chromosome Aberrations; Chromosomes, Human, 13-15; Chromosomes, Human, 6-12; Human; *Oncogenes; Review; Transcription Factors/*immunology; *Translocation (Genetics); Tumor Virus Infections/*immunology.

120. NEW GENETICS OF BURKITT'S LYMPHOMA AND OTHER NON-HODGKIN'S LYMPHOMAS

Aisenberg AC

Department of Medicine, Massachusetts General Hospital, Boston.
Am J Med; 77(6):1083-90 1984

Recent progress in cytogenetics and molecular genetics allows striking new insight into Burkitt's lymphoma. In this B cell tumor, the oncogene c-myc located on the long arm of chromosome 8 translocates to one of three locations: adjacent to the immunoglobulin heavy chain gene on chromosome 14, adjacent to the gene for the kappa light chain of immunoglobulin on chromosome 2, or adjacent to the gene for the

lambda light chain on chromosome 22. Nucleotide sequence analysis indicates that the translocated c-myc is usually upstream of an immunoglobulin constant region gene, although the exact position varies. In its new location, the oncogene is actively transcribed and may have escaped its normal control mechanisms. It can be no coincidence that this B cell lymphoma is intimately associated with a misadventure in the genetic underpinnings of the major event in B cell differentiation, the assembling of a functional immunoglobulin molecule. Similar genetic catastrophes probably account for the more common B cell lymphomas and could provide the basis of a coherent lymphoma classification. (49 Refs)

121. SOME QUESTIONS ON THE SIGNIFICANCE OF CHROMOSOME ALTERATIONS IN LEUKEMIAS AND LYMPHOMAS: A REVIEW

Neri G

Department of Medical Genetics, Shodair Children's Hospital, Helena, Montana.

Am J Med Genet; 18(3):471-81 1984

Recent improvement in the methods of chromosome analysis has allowed recognition of consistent chromosome alterations in several human cancers, especially leukemias and lymphomas. At the same time, newly discovered human cellular oncogenes have been mapped to individual chromosomes, with precise band assignment. Some of the assignments are coincident with the breakpoints of translocations observed in particular tumors. In fact, a relocation of the corresponding oncogenes has been observed in the cells of some of these tumors. Two notable examples are that of the t(9;22) translocation of chronic myelogenous leukemia (CML), causing the transfer of the oncogene c-abl from chromosome 9 to chromosome 22, and that of the t(8;14) translocation of Burkitt lymphoma, causing the transfer of the oncogene c-myc from chromosome 8 to chromosome 14. These findings can be taken as indicative of a critical role of chromosome alterations in the origin of cancer, through the activation of one or more cellular oncogenes, although there is no firm evidence that such an activation actually occurs. In addition, some concern exists over the validity of accepting in vitro transformation of a cell line by oncogenes as a model of carcinogenesis in man. For these reasons the question on the significance of chromosome alterations in leukemia and lymphomas should not be considered entirely settled yet. Useful models, whose study may lead to the clarification of this important point, are represented by premalignant conditions, such as the myeloproliferative disorders, where chromosome abnormalities are present before the development of a bona fide neoplasm, and by the aneuploidy syndromes, in which there exists an association between a constitutional chromosome anomaly and an increased risk of cancer.

122. ONCOGENES IN B-CELL NEOPLASIA (130 Refs)

Potter M, Musbinski JF

Laboratory of Genetics, National Cancer Institute, Bethesda, Maryland.

Cancer Invest; 2(4):285-300 1984

Keywords (MeSH): Abelson Leukemia Virus/genetics; Animal; Avian Leukosis Viruses/genetics; *B Lymphocytes; Base Sequence; Burkitt's Lymphoma/familial and genetic; Bursa of Fabricius; Chickens; Human; Lymphoma/etiology/*familial and genetic; Lymphosarcoma/familial and genetic; Mice; *Oncogenes; Plasmacytoma/familial and genetic; Review; Translocation (Genetics).

123. CHROMOSOME TRANSLOCATIONS AND B CELL NEOPLASIA

Croce CM, Tsujimoto Y, Erikson J, Nowell P
Wistar Institute of Anatomy and Biology, Philadelphia,
Pennsylvania.

Lab Invest; 51(3):258-67 1984

Keywords (MeSH): Adult; Animal; B Lymphocytes/*ultrastructure; Burkitt's Lymphoma/familial and genetic; Chromosomes, Human, 13-15; Chromosomes, Human, 16-18; Chromosomes, Human, 21-22; Chromosomes, Human, 6-12; DNA, Recombinant; Gene Expression Regulation; Genes, Viral; Human; Immunoglobulins, Heavy Chain/genetics; Leukemia/*familial and genetic; Lymphoma/*familial and genetic; Oncogenes; Retroviridae/genetics; Transcription, Genetic; *Translocation (Genetics).

124. ONCOGENE ACTIVATION AND TUMOR PROGRESSION (79 Refs)

Klein G, Klein E

Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.

Carcinogenesis; 5(4):429-35 1984

Keywords (MeSH): Animal; Burkitt's Lymphoma/familial and genetic; DNA, Neoplasm/genetics; Human; Mice; Neoplasms/familial and genetic/*physiopathology; *Oncogenes; Plasmacytoma/familial and genetic; Review; Skin Neoplasms/chemically induced/familial and genetic; Transfection; Translocation (Genetics).

125. CYTOGENETIC ABNORMALITIES IN LYMPHOID NEOPLASIA

Sandberg AA

Roswell Park Memorial Institute, Buffalo, NY 14263

Prog Cancer Res Ther; 27:263-82 1984

This is a retrospective study of chromosomal abnormalities associated with various types of leukemias and lymphomas. Burkitt's lymphoma and other Burkitt-type diseases are characterized by a translocation of material from chromosome 8 to 14. More detailed analyses of the Burkitt-type diseases has shown variant translocations. These occur between chromosomes 2 and 8 and chromosomes 8 and 22. The important factor seems to be the deletion in 8 at band q24. Secondary cytogenetic changes in Burkitt-type diseases are complex, with the partial trisomy of the long arm of chromosome 1 particularly common. Generally, the presence of secondary chromosome changes correlates with a more progressive course of the disease than in lymphomas without. In malignant non-Burkitt's lymphomas, the abnormality is most often an addition to chromosome 14, with the extra material usually coming from either chromosome 8, 18 or 1. Adult T-cell leukemias, studied more in Japan than in the West, show different chromosomal anomalies in different populations. Information on karyotypic findings in chronic lymphocytic leukemia (CLL) has just begun to be reported, primarily because of the introduction of a number of B-cell stimulants that have made it possible to obtain the leukemic cells in mitosis. To date the most common abnormality associated with CLL is trisomy of chromosome number 12. Chromosome changes in T-cell and Hodgkin's disease as yet are not well defined. Cytogenetically, acute lymphoblastic leukemia can be subdivided into several categories, each having a characteristic chromosome finding that can serve as a possible prognostic indicator. (80 Refs)

126. BIOLOGICAL IMPLICATIONS OF CONSISTENT CHROMOSOME REARRANGEMENTS IN LEUKEMIA AND LYMPHOMA (61 Refs)

Rowley JD

Department of Medicine, University of Chicago, Illinois.

Cancer Res; 44(8):3159-68 1984

Keywords (MeSH): Acute Disease; Basophils/physiology; Burkitt's Lymphoma/familial and genetic; *Chromosome Aberrations; *Chromosome Abnormalities; Chromosomes, Human/*physiology; Chromosomes, Human, 21-22; Human; Leukemia/*familial and genetic; Leukemia, Myelocytic/familial and genetic; Lymphoma/*familial and genetic; Oncogenes; Review; *Translocation (Genetics).

127. RECENT DEVELOPMENTS IN PLASMACYTOMAGENESIS IN MICE.

Potter M, Wiener F, Musbinski JF

Lab. of Genetics, Natl. Cancer Inst., Bethesda, MD 20205

Adv Viral Oncol; 4:139-62 1984

The development of Ig-secreting tumors (plasmacytomas or immunocytomas) presents an intriguing model system of oncogenesis because these tumor cells have retained the potential to both divide and secrete Ig. The biology of plasmacytogenesis in the mouse is reviewed, and the possible role of endogenous retroviruses in the pathogenesis, is discussed as is evidence that non-random chromosomal translocations and specific oncogenes are involved. Induction of plasmacytomas is by ip mineral oil injections and requires a long latent period. The genetic basis for susceptibility to pristane, mineral oils and plastics as inductive agents is reviewed and the immunological aspects of plasmacytogenesis are discussed. The three large families of endogenous retroviruses, discussed in terms of viral properties and their roles as mutagenic agents, are: (a) type C leukemia viruses, including xenotropic and ecotropic forms, (b) mammary tumor viruses (MTV), and (c) intracisternal A particles (IAP). Non-random chromosomal translocations and their occurrence in tumors are discussed at length with special emphasis on the role of the myc oncogene in these translocations. (105 Refs)

128. THE MYC ONCOGENE IN MOUSE PLASMACYTOMAGENESIS

Potter M

Laboratory of Genetics, National Cancer Institute, Bethesda, Md.

Surv Synth Pathol Res; 3(6):499-509 1984

Keywords (MeSH): Abelson Leukemia Virus; Animal; Chromosome Mapping; Chromosomes/ultrastructure; Gene Expression Regulation; Leukemia, Experimental/complications; Mice/*genetics; Mineral Oil; *Oncogenes; Plasmacytoma/chemically induced/etiology/*familial and genetic; Plastics; Terpenes; Translocation (Genetics).

129. C-MYC INVOLVEMENT IN CHROMOSOMAL TRANSLOCATIONS IN MICE AND MEN (115 Refs)

Caccia NC, Mak TW, Klein G

Ontario Cancer Institute, Toronto, Canada.

J Cell Physiol Suppl; 3:199-208 1984

Keywords (MeSH): Animal; B Lymphocytes; Burkitt's Lymphoma/*familial and genetic; Chromosome Abnormalities/familial and genetic; Chromosomes, Human, 1-3; Chromosomes, Human, 13-15; Chromosomes, Human, 6-12; Gene Amplification; *Genes; Human; Immunoglobulins/genetics; Kidney Neoplasms/familial and genetic; Leukemia, Myelocytic/familial and genetic; Mice; Operon; Plasmacytoma/*familial and genetic; Review; *Translocation (Genetics); Trisomy.

130. TUMOURS OF LYMPHOCYTES. WHAT HAPPENS WHEN CELLULAR ONCOGENES COLLIDE WITH IMMUNOGLOBULIN GENES

Rokertson M

No affiliation given

Nature; 302(5908):474 1983

Research on lymphocyte malignancies and on immunoglobulin genes that undergo rearrangements is reviewed; the possibility that events leading to malignancy in some B-cell lymphomas might represent some kind of travesty of genetic rearrangements underlying the normal differentiation of B lymphocytes is discussed. The underlying mechanism might be explained by the nature of the 5' exon of the intact c-myc gene. Although the exon is transcribed in normal cells, it does not code for protein since it contains several stop codons that clearly prohibit its translation. It is possible that the existence of this long untranslated region may greatly reduce the efficiency of translation of the two functional exons, so that its removal increases translational efficiency and results in the synthesis of more myc product with little increase in myc transcription. The effect of this scheme in Burkitt's lymphoma is unclear since in some cases the truncated gene does not appear to be transcribed at all in tumor cells while in others a truncated transcript is produced from a c-myc gene that has been translocated intact. Thus, there is more than one c-myc potentiation to the production of a tumor cell. (11 Refs)

131. TRANSLOCATIONS AMONG ANTIBODY GENES IN HUMAN CANCER

Leder P, Battey J, Lenoir G, Moulding C, Murphy W, Potter H, Stewart T, Taub R

Department of Genetics, Harvard Medical School, Boston, Massachusetts

Science; 222(4625):763-71 1983

The characteristic chromosomal translocations that occur in certain human malignancies offer opportunities to understand how two gene systems can affect one another when they are accidentally juxtaposed. In the case of Burkitt lymphoma, such a translocation joins the cellular oncogene, c-myc, to a region encoding one of the immunoglobulin genes. In at least one example, the coding sequence of the rearranged c-myc gene is identical to that of the normal gene, implying that the gene must be quantitatively, rather than qualitatively, altered in its expression if it is to play a role in transformation. One might expect to find the rearranged c-myc gene in a configuration that would allow it to take advantage of one of the known immunoglobulin promoters or enhancer elements. However, the rearranged c-myc gene is often placed so that it can utilize neither of these structures. Since the level of c-myc messenger RNA is often elevated in Burkitt cells, the translocation may lead to a deregulation of the c-myc gene. Further, since the normal allele in a Burkitt cell is often transcriptionally silent in the presence of a rearranged allele, a model for c-myc regulation is suggested that involves a trans-acting negative control element that might use as its target a highly conserved portion of the c-myc gene encoding two discrete transcriptional promoters. (46 Refs)

132. SPECIFIC CHROMOSOMAL TRANSLOCATIONS AND THE GENESIS OF B-CELL-DERIVED TUMORS IN MICE AND MEN

Klein G

Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm, Sweden
Cell; 32(2):311-315 1983

Recent findings are reported that lend a molecular basis to the oncogene-activation hypothesis and also prove the homology of the murine plasmacytomas (MPC) and human

Burkitt's lymphomas (BL). The potential importance of the translocations for the pathogenesis of BL is emphasized by the fact that all adequately analyzed cases of confirmed BL, whether carrying Epstein-Barr virus or not, carry one of three characteristic chromosomal markers, generated by translocation of the distal fragment of chromosome 8 (breakpoint: q24) to one of three Ig-gene-carrying chromosomes. Involvement of the IgH locus and identification of c-myc as the transposed oncogene in BL are described. Molecular studies of MPC are described. The role of the myc rearrangement in 15-trisomic murine leukemias is described. An additional target cell can be found in the rat. In human BL and the MPC system, the competing concepts of elevated vs altered myc transcription will have to be evaluated in relation to tumorigenicity. Further analysis of the MPC/BL system may also provide models to look into the possible significance of oncogene activation by genetic transposition in the genesis of other tumors. (no Refs)

133. IDENTIFICATION OF THE CONSTANT CHROMOSOME REGIONS INVOLVED IN HUMAN HEMATOLOGIC MALIGNANT DISEASE

Rowley JD

Dept. Medicine, Univ. Chicago, Chicago, IL, 60637

Science; 216(4547):749-751 1982

Specific consistent chromosome translocations are regularly observed in certain human leukemias and lymphomas. For the myeloid leukemias, the constant recombinants are: the long arm of 9 to chromosome 22 in chronic myeloid leukemia, the long arm of 21 to chromosome 8 in acute myeloblastic leukemia, and the long arm of 17 to chromosome 13 in acute promyelocytic leukemia. Three related translocations are seen in Burkitt lymphoma and B cell acute lymphocytic leukemia; in each one, chromosome 8 is involved with chromosome 2, 14, or 22. Analysis of a complex translocation affecting chromosomes 8 and 14 indicates that the translocation of chromosome 8 to chromosome 14 is the critical constant rearrangement. The analysis of the DNA at the translocation sites of these chromosomes, rather than the reciprocal of each translocation, appears to be the most productive focus for initial study. The various immunoglobulin loci are located on chromosomes 2, 14, and 22, the chromosomes regularly involved in translocations in Burkitt lymphoma and B cell acute lymphocytic leukemia. (Author abstract) (30 Refs)

134. CHROMOSOME ABNORMALITIES IN MALIGNANT HEMATOLOGIC DISEASES

Rowley JD, Testa JR

Franklin McLean Memorial Res. Inst., Univ. Chicago, Chicago, IL, 60637

Adv Cancer Res; 36:103-148 1982

Recent results in the study of the role of chromosome abnormalities in malignant hematologic diseases are reviewed. Chromosome abnormalities associated with chronic myelogenous leukemia, acute nonlymphocytic leukemia (ANLL), acute lymphocytic leukemia, and polycythemia vera are described, and the implications of nonrandom changes for malignant transformation are discussed. The relatively consistent chromosome changes, especially specific translocations, that are closely associated with particular neoplasms provide convincing evidence for the fundamental role of these changes in the transformation of a normal cell to a malignant one. The number of nonrandom changes that are seen in a cancer such as ANLL suggests that a class of genes is involved. Human gene mapping makes it possible to relate the chromosomes affected by chromosome changes associated with neoplasia to specific genes they carry. Preliminary results showed that chromosomes with genes associated with nucleic

acid biosynthesis, and specific regions of the chromosomes bearing these genes, were frequently involved in rearrangements associated with hematologic cancers. The goal of future studies must be to show how chromosome changes provide selected cells in certain persons with a growth advantage resulting in malignancy. (175 Refs)

135. TRANSLOCATIONS INVOLVING IG-LOCUS-CARRYING CHROMOSOMES: A MODEL FOR GENETIC TRANSPOSITION IN CARCINOGENESIS

Klein G, Lenoir G

Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden

Adv Cancer Res; 37:381-387 1982

The role of chromosomal translocations involving immunoglobulin loci in carcinogenesis is reviewed. Analysis of cellular transformation by retroviruses indicates that the retrovirus provides genetic material for integration and constitutive activation of a transforming oncogene. Transformation may apparently result from production of a normal protein in excessive amounts, at the wrong time, or in the wrong place. A slow-acting, nontransforming, nondefective avian leukosis virus activates the cellular counterpart of a viral oncogene by inserting long terminal repeat sequence in proximity to the oncogene. The ability of cellular oncogenes to cross tissue boundaries and to show strong evolutionary conservation indicates that these oncogenes may have a role in normal cell function. Studies of murine plasmacytoma and Burkitt's lymphoma have demonstrated that these diseases require a specific chromosomal translocation (or a variant translocation) that brings a part of the distal segment of chromosome 8 into proximity with a functionally active immunoglobulin-producing locus. The immunoglobulin locus is probably active in the malignant cell. New methods of transfection make possible characterization of oncogenes associated with tumors that carry translocations. (42 Refs)

136. THE ROLE OF GENE DOSAGE AND GENETIC TRANSPOSITIONS IN CARCINOGENESIS

Klein G

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Nature; 293(5839):313-318 1981

Analysis of chromosome translocations associated with B-cell derived tumors and studies of chromosome-15 trisomy in murine leukemia support the theory, emerging from recent work on tumor viruses, that cancer can be associated with DNA rearrangements which result in the increased expression of normal cellular genes. (Author abstract) (87 Refs)

B.

ABL ONCOGENE TRANSLOCATIONS

1.

Abl Translocations and Chronic Myelogenous Leukemia

137. HETEROGENEITY OF CHROMOSOME 22 BREAKPOINT IN PHILADELPHIA-POSITIVE (PH+) ACUTE LYMPHOCYTIC LEUKEMIA

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Proc Natl Acad Sci USA; 83(6):1807-11 1986

In chronic myelogenous leukemias (CML) with the t(9;22)(q34;q11) chromosome translocation the breakpoints on chromosome 22 occur within a 5.8-kilobase segment of DNA referred to as 'breakpoint cluster region' (bcr). The same cytogenetically indistinguishable translocation occurs in

approximately 10% of patients with acute lymphocytic leukemia (ALL). In this study we have investigated the chromosome breakpoints in several cases of ALL carrying the t(9;22) translocation. In three of five cases of ALL we found that the bcr region was not involved in the chromosome rearrangement and that the 22q11 chromosome breakpoints were proximal (5') to the bcr region at band 22q11. In addition, we observed normal size bcr and c-abl transcripts in an ALL cell line carrying the t(9;22) translocation. We conclude, therefore, that if c-abl is inappropriately expressed in ALL cells without bcr rearrangements, the genetic mechanism of activation must be different from that reported for CML.

138. SECONDARY ACTIVATION OF C-ABL MAY BE RELATED TO TRANSLOCATION TO THE NUCLEOLAR ORGANIZER REGION IN AN IN VITRO CULTURED RAT LEUKEMIA CELL LINE (K3D)

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Proc Natl Acad Sci USA; 83(4):1079-83 1986

Localization of cellular oncogenes (c-onc) near the break points of translocations in tumor cells has indicated involvement of these genes in neoplastic growth. Enhanced transcription of the cellular homolog (c-abl) of the transforming sequence of Abelson murine leukemia virus was observed in K3D, which was one of the cloned cell lines of 7,12-dimethylbenz[a]anthracene-induced rat erythroblastic leukemia. Since the c-abl activation was not observed in the parent cell line (K2D) from which K3D was derived and the latter was different from the former in the presence of a new marker chromosome, t(3;12), this marker may play a role in the expression of c-abl in K3D cells. In contrast to the human c-onc assignments, few rat c-onc assignments have been reported. In situ molecular hybridization studies assigned c-abl to the 3q12 site of the normal chromosome 3 and to the break point of the translocation t(3;12) in K3D cells. Another break point in this translocation chromosome 12p11 involves the nucleolar region, and the 3;12 translocation may involve c-abl and nucleolar cistrons. These results provide evidence of secondary c-onc activation during karyotypic evolution of cloned malignant cells.

139. C-SIS AND C-ABL EXPRESSION IN CHRONIC MYELOGENOUS LEUKEMIA AND OTHER HEMATOLOGIC MALIGNANCIES

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Blood; 67(3):839-41 1986

Cellular oncogenes have been localized at the breakpoints of characteristic chromosomal rearrangements occurring in certain hematologic malignancies. This has been reported to result in aberrant expression of the involved oncogenes. Over 90% of chronic myelogenous leukemia (CML) is characterized by a reciprocal translocation that brings c-abl from chromosome 9 to chromosome 22, and c-sis from chromosome 22 to chromosome 9. To investigate the possible role of these two oncogenes in the leukemic process, we studied their expression in a number of fresh samples obtained from patients with various forms of leukemia, by Northern blot analysis using c-onc probes. Seven of 24 samples obtained from patients with either CML or chronic myelomonocytic leukemia expressed a normal 4.0-kilobase (kb) c-sis transcript. C-sis expression was found only in the accelerated/blast phases but not in the chronic phase of CML. All of the CML Philadelphia chromosome-positive (Ph1+) samples ex-

pressed an aberrant 8-kb c-abl transcript. The expression of c-sis in

140. GENOMIC DIVERSITY CORRELATES WITH CLINICAL VARIATION IN PH⁺-NEGATIVE CHRONIC MYELOID LEUKAEMIA

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Nature; 320(6059):281-3 1986

The Philadelphia chromosome (Ph⁺) is found in the blood cells of about 90% of patients with chronic myeloid leukaemia (CML) and usually results from the reciprocal chromosome translocation t(9;22). This translocation relocates the proto-oncogene c-abl, normally found on chromosome 9q34, to within the breakpoint cluster region (bcr) on chromosome 22q11 (refs 3-8). The juxtaposition of c-abl and the 5' portion of bcr appears to be the critical genomic event in CML and results in a novel 8-kilobase (kb) fused abl/bcr transcript and a c-abl-related protein of relative molecular mass 210,000 (ref.11). About 10% of adult patients diagnosed as CML lack the Ph⁺ chromosome; they represent a heterogeneous group of disorders which are difficult to diagnose precisely. We have examined five patients with CML whose leukaemic cells have a normal karyotype. We report here that two of the patients showed the same genomic change as occurs in Ph⁺-positive CML, but the change resulted from a mechanism other than chromosomal translocation. The remaining three patients showed no genomic rearrangement. This genomic diversity correlated with the clinical differences between the patients.

141. ADDITIONAL C-ABL/BCR REARRANGEMENTS IN A CML PATIENT EXHIBITING TWO PH⁺ CHROMOSOMES DURING BLAST CRISIS

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Leuk Res; 10(2):221-5 1986

Recent data suggest that two human genes, c-abl on chromosome 9 and bcr on chromosome 22, are involved in the generation of Ph⁺-positive CML. To examine a possible role of these sequences in transition from chronic towards blastic phase, rearrangements within bcr were analysed in 4 patients with Ph⁺-positive CML during chronic and acute phase. In 3 patients bcr rearrangements were identical in both phases, while in a fourth patient with duplicated Ph⁺ an amplified additional bcr fragment was detected in acute phase. Northern blot analysis of blast cells of the latter patient showed a novel 10.3 kb RNA species that replaced the altered 8 kb RNA transcript usually found in Ph⁺-positive CML.

142. EXPRESSION OF A TRANSLOCATED C-ABL GENE IN HYBRIDS OF MOUSE FIBROBLASTS AND CHRONIC MYELOGENOUS LEUKAEMIA CELLS

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Nature; 319(6051):331-3 1986

Chronic myelogenous leukaemia (CML) is a clonal disease arising from malignant transformation of pluripotent hematopoietic stem cells. In most cases, it is characterized by the presence of the Philadelphia (Ph⁺) chromosome (22q-) which results from a reciprocal translocation between chromosomes 9 and 22 (refs 1-3). In this translocation, the human homologue of the Abelson virus oncogene, c-abl, normally on chromosome 9, is moved to chromosome 22, while c-sis, the

cellular homologue of the simian sarcoma virus oncogene, is moved from chromosome 22 to chromosome 9 (refs 4-6). CML cells carrying the t(9;22) chromosomal translocation are known to produce an 8-kilobase (kb) c-abl transcript in addition to the normal 6- and 7-kb transcripts and to express the normal p145 abl protein and a p210 c-abl protein possessing a tyrosine kinase activity not detected in the p145 species. Results of our analyses using somatic cell hybrids between a mouse fibroblast line and two human CML-derived cell lines which carry the Ph⁺ chromosome and are phenotypically identical to the fibroblast parent indicate that only the hybrid cells containing Ph⁺ chromosome express both the 8-kb c-abl RNA and the p210 protein. Thus, expression of the altered c-abl transcripts and protein depends on the presence of the Ph⁺ chromosome and is not myeloid-specific.

143. THE HUMAN CELLULAR ABL GENE PRODUCT IN THE CHRONIC MYELOGENOUS LEUKEMIA CELL LINE K562 HAS AN ASSOCIATED TYROSINE PROTEIN KINASE ACTIVITY

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Virology; 140(2):230-8 1985

Three antisera against the mouse v-abl gene product were used to identify two potential human c-abl gene products in the chronic myelogenous leukemia cell line K562. Two anti-peptide sera were generated in rabbits using the predicted amino acid sequence of the mouse v-abl gene product. One antiserum was made against a polypeptide overlapping the in vivo tyrosine phosphorylation site of murine P120gag-abl and what is believed to be a homologous tyrosine phosphorylation site of the predicted normal human c-abl gene product (v-abl 263-280). The second anti-peptide serum, abl 389-403, was generated against a predicted hydrophilic peptide of the v-abl gene product. Immunoprecipitation from K562 cells metabolically labeled with [³²P]orthophosphate by a mouse tumor regressor and abl 389-403 anti-peptide sera detected two proteins of 190,000 and 240,000 Da. Both proteins were labeled primarily at serine and, to a much lesser extent, at tyrosine residues. Immune complex kinase assays using conditions that allow the tyrosine phosphorylation of P120gag-abl showed that in vitro phosphorylation of P190 and P240 occurs primarily at tyrosine residues. The detection of these enzymatically active human c-abl gene products is a rare observation which may be in part attributed to the c-abl gene translocation from chromosomes 9 to 22 occurring in the vast majority of chronic myelogenous leukemia patients.

144. ACTIVATION OF THE C-ABL ONCOGENE BY VIRAL TRANSDUCTION OR CHROMOSOMAL TRANSLOCATION GENERATES ALTERED C-ABL PROTEINS WITH SIMILAR IN VITRO KINASE PROPERTIES

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Mol Cell Biol; 5(1):204-13 1985

The v-abl protein of Abelson murine leukemia virus is a tyrosine-specific kinase. Its normal cellular homolog, murine c-abl, does not possess detectable tyrosine kinase activity in vitro. Previously, we have detected tyrosine kinase activity in vitro for an altered c-abl gene product (c-abl P210) in the K562 human chronic myelogenous leukemia cell line. The expression of this variant c-abl gene product correlates with chromosomal translocation and amplification of the c-abl gene in K562 cells. Like v-abl, c-abl P210 is a fusion protein containing non-abl sequences near the amino terminus of c-

abl. We compared the in vitro tyrosine kinase activity of c-abl P210 with that of wild-type murine v-abl. The remarkable similarities of these two proteins with respect to cis-acting autophosphorylation, trans-acting phosphorylation of exogenous substrates, and kinase inhibition, using site-directed abl-specific antisera, suggested that c-abl P210 could function similarly to v-abl in vivo. In addition, c-abl P210 possessed an associated serine kinase activity in immunoprecipitates. The serine kinase activity was not inhibited by site-directed, abl-specific antisera that inhibit the tyrosine kinase activity, suggesting that the serine kinase activity is not an intrinsic property of c-abl P210. Thus, the activation of the c-abl gene in a human leukemia cell line may have functional consequences analogous to activation of the c-abl gene in Abelson murine leukemia virus.

143. CELL LINES AND CLINICAL ISOLATES DERIVED FROM PH1-POSITIVE CHRONIC MYELOGENOUS LEUKEMIA PATIENTS EXPRESS C-ABL PROTEINS WITH A COMMON STRUCTURAL ALTERATION
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Proc Natl Acad Sci USA; 82(6):1810-4 1985

The Philadelphia chromosome (Ph1), observed in greater than 90% of chronic myelogenous leukemia (CML) patients, results from a specific chromosomal translocation involving the c-abl gene. The translocation breakpoint occurs near c-abl and correlates with the production of an altered c-abl mRNA. In the CML-derived cell line K562, Ph1 is accompanied by a structurally altered c-abl protein (P210c-abl) with in vitro tyrosine kinase activity not detected with the normal c-abl protein (P145c-abl). We have examined c-abl proteins in other Ph1-positive CML cell lines and found that they all express P210c-abl. P210c-abl was also detected in bone marrow cells from CML patients with Ph1 in the accelerated and blast crisis phases of the disease. Comparison of the [35S]methionine-labeled tryptic peptides generated from the normal P145c-abl and P210c-abl showed that they have closely related structures, but additional polypeptide sequences are present in P210c-abl. Based on these results we propose that translocation of c-abl in Ph1-positive CML results in the creation of a chimeric gene leading to the production of a structurally altered c-abl protein with activated tyrosine kinase activity. The altered P210 c-abl protein is strongly implicated in the pathogenesis of CML.

146. ASSOCIATION BETWEEN THE PHILADELPHIA CHROMOSOME AND A UNIQUE ABL TRANSCRIPT
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Hematol Bluttransfus; 29:154-8 1983

Keywords (MeSH): *Chromosomes, Human, 21-22; Comparative Study; Hela Cells/analysis; Human; Leukemia/*familial and genetic; Leukemia, Myeloblastic/*familial and genetic; Leukemia, Myelocytic/*familial and genetic; Molecular Weight; *Oncogenes; RNA, Neoplasm/isolation and purification; *Transcription, Genetic.

147. C-ABL AND BCR ARE REARRANGED IN A PH1-NEGATIVE CML PATIENT
Bartram CR, Kleihauer E, de Klein A, Grossfeld G, Teyssier JR, Heisterkamp N, Groffen J
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EMBO J; 4(3):683-6 1985

Chromosomal analysis of a patient with chronic myelocytic leukemia (CML) revealed a translocation (9;12) (q34;q21) without a detectable Philadelphia chromosome (Ph1). Using

molecular approaches we demonstrate (i) a rearrangement within the CML breakpoint cluster region (bcr) on chromosome 22, and (ii) a joint translocation of bcr and c-abl oncogene sequences to the derivative chromosome 12. These observations support the view that sequences residing on both chromosome 9 (c-abl) and 22 (bcr) are involved in the generation of CML and suggest that a subset of Ph1-negative patients may in fact belong to the clinical entity of Ph1-positive CML.

148. BCR REARRANGEMENT WITHOUT JUXTAPOSITION OF C-ABL IN CHRONIC MYELOCYTIC LEUKEMIA

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J Exp Med; 162(6):2173-9 1985

Southern blot analysis detected a bcr gene rearrangement within leukemic cells of a Philadelphia chromosome-negative chronic myelocytic leukemia (CML) patient that led to transcription of a novel 7.3 kb bcr RNA species. Participation of the c-abl oncogene in this genomic recombination could be ruled out by in situ hybridization studies and Northern blot analysis.

149. EVIDENCE OF A NEW CHIMERIC BCR/C-ABL MRNA IN PATIENTS WITH CHRONIC MYELOCYTIC LEUKEMIA AND THE PHILADELPHIA CHROMOSOME

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N Engl J Med; 313(23):1429-33 1985

The hallmark of chronic myelocytic leukemia is the presence of the Philadelphia chromosome (Ph1). In recent studies, we obtained data that strongly suggested the involvement of an oncogene, c-abl, in this type of leukemia. This oncogene, normally located on chromosome 9, is translocated to chromosome 22 as a result of the Ph1 translocation. In addition, we identified a region on chromosome 22, the breakpoint cluster region (bcr), which contains the chromosomal breakpoint in all patients with chronic myelocytic leukemia who are positive for Ph1. Recent studies have suggested that the bcr is part of a gene that is truncated as a consequence of the Ph1 translocation. The deleted part of this gene could be replaced by c-abl sequences; to test this hypothesis we analyzed the RNA of five patients with chronic myelocytic leukemia. All five had chimeric bcr/c-abl messenger RNA, suggesting that the deleterious effects of this disease can be associated with an abnormal chimeric protein encoded by the bcr and the c-abl oncogene.

150. FUSED TRANSCRIPT OF ABL AND BCR GENES IN CHRONIC MYELOGENOUS LEUKAEMIA

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Nature; 315(6020):550-4 1985

Human chronic myelogenous leukaemia is characterized by a reciprocal translocation between chromosomes 9 and 22 resulting in an abbreviated form of chromosome 22 and the transfer of the abl cellular oncogene from chromosome 9 into the bcr gene of chromosome 22. Characterization of an 8-kilobase RNA specific to chronic myelogenous leukaemia shows it to be a fused transcript of the two genes. The fused protein that would be produced is probably involved in the malignant process.

151. STRUCTURAL ORGANIZATION OF THE BCR GENE AND ITS ROLE IN THE PH⁺ TRANSLOCATION

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Nature; 315(6022):758-61 1985

The Philadelphia (Ph⁺) chromosome, an abnormal chromosome 22 (ref. 1), is one of the best-known examples of a specific human chromosomal abnormality strongly associated with one form of human leukaemia, chronic myelocytic leukaemia (CML). The finding that a small region of chromosome 9 which includes the c-abl oncogene is translocated to chromosome 22 prompted studies to elucidate the molecular mechanisms involved in this disease. We have demonstrated previously that the chromosome 9 of one patient with CML contains a breakpoint 14 kilobases (kb) 5' of the most 5' v-abl-homologous exon. These data suggest a role for c-abl in CML, a theory supported by the presence of an abnormally sized abl messenger RNA and protein in the CML cell line K562. The region involved in the translocation on chromosome 22 has also been identified: all Ph⁺-positive patients examined to date have a breakpoint within a 5.8-kb region, for which we have proposed the name 'breakpoint cluster region' (bcr). To determine whether bcr contains protein-encoding regions, probes from bcr were tested for their ability to hybridize to complementary DNA sequences. A 0.6-kb HindIII/BamHI bcr restriction enzyme fragment proved suitable for isolating several cDNA clones from a human fibroblast cDNA library. Using bcr cDNA sequences, we obtained data strongly suggesting the presence of a chimeric bcr/abl mRNA in the leukaemic cells of Ph⁺-positive CML patients. The recent isolation of cDNA clones containing bcr and abl sequences confirms this finding. Because the bcr part of the chimeric mRNA could be required to induce the transforming activity of the human c-abl oncogene, we have now initiated studies to characterize the normal 'bcr gene' and to determine the effect of a translocation within its coding domain. We demonstrate that as a result of the Ph⁺ translocation, a variable number of bcr exons are included in the chimeric bcr/abl mRNA. The bcr gene sequences in this mRNA could be responsible for the transition of the abl cellular proto-oncogene into an oncogene.

152. TRANSLOCATION OF C-ABL TO 'MASKED' PH IN CHRONIC MYELOID LEUKEMIA

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Cancer Genet Cytogenet; 18(2):95-104 1985

In two patients with chronic myeloid leukemia (CML), the nature of the chromosomal rearrangement giving rise to 'masked' Ph has been studied by in situ hybridization of human c-abl sequences. The c-abl probes hybridized to the 22q11 region of the 'masked' Ph, demonstrating that translocation of sequences from 9q34 to the Ph did occur exactly as in standard Ph or in other types of variants previously studied. These results provide additional evidence for the occurrence of a constant molecular rearrangement in Ph-positive CML.

153. PHILADELPHIA TRANSLOCATION AND THE HUMAN C-ABL ONCOGENE - RELATIONS IN THE LIGHT OF MOLECULAR GENETICS

Bartram CR, Grussel G
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Klin Padiatr; 197(3):196-202 1985

Application of recombinant DNA techniques led to the characterization of a heterogenous group of evolutionary conserved genes with potential transforming activity, called on-

cogenes. Regularly they seem to be involved in normal cell proliferation and differentiation. Various mechanisms including an increased dosage of gene product as well as subtle point mutations activate these sequences to oncogenes *sensu strictu*. Molecular analysis of the Philadelphia translocation in leukemic cells of CML-patients revealed a consistent translocation of the human c-abl-oncogene from chromosome 9 to the Ph1-chromosome, regardless of the cytogenetic subtype. Moreover we could demonstrate individual breakpoints for every patient investigated so far. However, these breakpoints are clustered on chromosome 22 within sequences of the bcr-gene. In leukemic cells containing the rearranged-c-abl/bcr sequences a new transcript is detected which is possibly the mRNA for an altered c-abl-protein that unmasks associated tyrosine specific kinase activity. These gene rearrangements were not detected in Ph1-negative CML-patients. Another human oncogene, c-sis, is located on chromosome 22, but seems not to play a crucial role in the generation of CML. These results are discussed in the context of recent advances in oncogene-research.

154. VARIABLE BREAKPOINTS ON THE PHILADELPHIA CHROMOSOME IN CHRONIC MYELOGENOUS LEUKEMIA

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Blood; 66(1):243-5 1985

The abl oncogene is translocated from chromosome 9 to 22 in the creation of the Philadelphia (Ph1) chromosome. This article describes new translocation breakpoints identified in two patients with chronic myelogenous leukemia using Southern blotting and cloned human DNA probes from chromosome 9. The translocation breakpoints on chromosome 9 in both of these patients lie closer to the human cellular abl (c-abl) gene, and the chromosome 22 breakpoints are distributed more widely than previously reported. These data help to define more clearly the chromosomal span of the breakpoints and indicate that some translocations include very little chromosome 9 sequence located 5' to the c-abl gene.

155. 'MASKED' PH1-CHROMOSOME IN CHRONIC MYELOGENOUS LEUKAEMIA (CML)

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Blut; 50(3):129-33 1985

The CML patients with so called masked Ph1-chromosome have been reviewed. Although the importance of c-sis and c-abl oncogenes is gaining popularity yet their role in the genesis of CML remain obscure. Patients with masked Ph1-chromosomes where chromosome 9 is not involved in the translocation(s) will provide a clue to the role of c-abl and/or c-sis in oncogenesis.

156. CHROMOSOMAL LOCALIZATION AND CHARACTERIZATION OF C-ABL IN THE T(6;9) OF ACUTE NONLYMPHOCYTIC LEUKEMIA

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Proc Natl Acad Sci USA; 82(24):8742-6 1985

Acute nonlymphocytic leukemia associated with the chromosomal translocation t(6;9)(p23;q34) is an entity that is frequently associated with basophilia, which it shares with chronic myelogenous leukemia. The breakpoint on chromosome 9, q34, appears to be cytogenetically identical in both malignancies and is the site of the cellular oncogene c-abl.

We investigated the role of c-abl in cells from two patients with the t(6;9) using in situ chromosomal hybridization, Southern hybridization, and in vitro phosphorylation. We showed that c-abl is not translocated from chromosome 9, resulting in a breakpoint that is on the 3' side of this gene. The t(6;9) translocation does not appear to result in the production of an aberrantly sized protein product or in the acquisition of in vitro tyrosine kinase activity. This is in direct contrast to the findings in chronic myelogenous leukemia, in which c-abl is translocated, leading to the production of a structurally altered c-abl protein with activated tyrosine kinase. Lastly, we demonstrated that the cells of one patient contain sequences from chromosome 9 inserted at the junction of a reciprocal translocation between chromosomes 4 and 10 on the 4q+ chromosome. This insertion, which is at least 100 kilobase pairs in length, represents a duplication and translocation of the protein coding region of c-abl.

157. VARIANT PH TRANSLOCATIONS IN CHRONIC MYELOID LEUKEMIA

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Cancer Genet Cytogenet; 18(3):215-27 1985

Variant translocations were found in eight of 142 consecutive patients with Ph-positive, chronic myeloid leukemia encountered in our laboratory during the last decade. Two patients had simple, two-way variant translocations: t(17;22)(p13;q11) and t(16;22)(q24;q11). Both of these patients had an additional translocation involving chromosomes : t(7;9)(q22;q34) and t(9;17)(q34;q21), respectively. Complex variant translocations were found in four cases: t(2;9;22)(p23q12;q34;q11), t(3;9;22)(p21;q34;q11), t(9;12;22)(q34;q13;q11q13), and t(13;17;22)(p11;p11q21;q11). In two cases, the only discernable cytogenetic aberration was del(22)(q11). A review of the chromosomal breakpoints involved in this series and in 185 cases of variant Ph translocations previously reported in the literature reveals that a disproportionately large number of breakpoints are located in light-staining regions of G-banded chromosomes. Furthermore, the breakpoints in simple variant translocations are more often located in terminal chromosomal regions, whereas, the breakpoints in complex translocations typically affect nonterminal bands. No obvious correlation was detected between variant Ph translocation breakpoints and either fragile sites, oncogene locations, or consistent chromosome breakpoints in other malignancies.

158. AN 8-KILOBASE A3L RNA TRANSCRIPT IN CHRONIC MYELOGENOUS LEUKEMIA

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Proc Natl Acad Sci USA; 81(18):5648-52 1984

Chronic myelogenous leukemia (CML) is a clonal hematologic malignancy characterized by a reciprocal translocation between chromosomes 9 and 22 [t(9;22)] in greater than 90% of cases. This translocation results in a short chromosome 22, termed the Philadelphia (Ph1 or 22q-) chromosome. Recently, the cellular oncogenes abl and sis were mapped to human chromosomes 9 and 22, respectively. Moreover, abl was shown to be translocated from chromosome 9 to 22 and sis from chromosome 22 to 9 in CML patients with t(9;22). These findings raised the possibility that one or both of these oncogenes is activated and directly involved in the development of the disease. We analyzed expression of the abl and sis oncogenes in leukemic cells from CML patients with t(9;22). We found that sis is not expressed but that abl is transcribed into an 8-kilobase RNA. This abl RNA is also

present in two leukemic cell lines (EM2 and K562), which were derived from CML patients and contain the t(9;22). This 8-kilobase RNA is not detected in normal cells, in other human leukemias without t(9;22), or in human cell lines that lack t(9;22). The consistent presence of this abl RNA transcript in CML with t(9;22) suggests that it is a consequence of abl translocation and that it plays a role in the development of this leukemia.

159. THE HUMAN C-ABL ONCOGENE IN THE PHILADELPHIA TRANSLOCATION

Groffen J, Stephenson JR, Heisterkamp N, Bartram C, de Klein A, Grossfeld G
Laboratory of Viral Carcinogenesis, National Cancer Institute-Fredrick Cancer Research Facility, Maryland.
J Cell Physiol Suppl; 3:179-91 1984

Keywords (MeSH): Animal; Base Sequence; Chromosome Banding; Chromosomes, Human, 21-22; Cloning, Molecular; Cricetus; DNA/analysis; Gene Amplification; Hamsters; Human; Leukemia, Myelocytic/*familial and genetic; Mice; Nucleic Acid Hybridization; *Oncogenes; *Translocation (Genetics).

160. IS THE CHROMOSOMAL REGION 9Q34 ALWAYS INVOLVED IN VARIANTS OF THE PH1 TRANSLOCATION?

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Cancer Genet Cytogenet; 13(1):1-16 1984

Six variants of the Ph1 translocation are described. The clinical diagnoses were chronic myeloid leukemia (CML) in 5 cases (patients 1-5) and acute lymphocytic leukemia (ALL) in patient 6. Three Ph1 variants were clear complex translocations, involving chromosomes , , and a third chromosome, i.e., , , or . The other three Ph1 variants appeared as 'simple' translocations between chromosome and chromosome , , or when G- or Q-banding were used. When studied with high resolution R-banding, a small deletion of the terminal part of one chromosome was visible, strongly suggesting that these variants were also complex translocations, i.e., t(9;19;22)(q34;p13;q11), t(4;9;22)(p16;q34;q11), and t(9;12;22)(q34;p13;q11). In the latter two cases, using in situ hybridization techniques, we demonstrated the presence of c-abl sequences on the Ph1 chromosome. This proved the involvement of 9q34 in these two variants. Our proposal is that most, and probably all, variants of Ph1 are complex translocations involving part of 9q34 and that the conjunction of a specific region of 22q11 with a specific segment of 9q34 (carrying the c-abl protooncogene) is essential for the development of Ph1 + CML.

161. PHILADELPHIA CHROMOSOMAL BREAKPOINTS ARE CLUSTERED WITHIN A LIMITED REGION, BCR, ON CHROMOSOME 22

Groffen J, Stephenson JR, Heisterkamp N, de Klein A, Bartram CR, Grossfeld G
Laboratory of Viral Carcinogenesis, National Cancer Institute-FCRF, Frederick, Maryland.
Cell; 36(1):93-9 1984

We have identified and molecularly cloned 46 kb of human DNA from chromosome 22 using a probe specific for the Philadelphia (Ph1) translocation breakpoint domain of one chronic myelocytic leukemia (CML) patient. The DNAs of 19 CML patients were examined for rearrangements on chromosome 22 with probes isolated from this cloned region. In 17 patients, chromosomal breakpoints were found within a limited region of up to 5.8 kb, for which we propose the

term 'breakpoint cluster region' (bcr). The two patients having no rearrangements within bcr lacked the Ph⁺ chromosome. The highly specific presence of a chromosomal breakpoint within bcr in Ph⁺-positive CML patients strongly suggests the involvement of bcr in this type of leukemia.

162. ALTERED TRANSCRIPTION OF AN ONCOGENE IN CHRONIC MYELOID LEUKAEMIA

Canaani E, Gale RP, Steiner-Saltz D, Berrebi A, Agbai E, Januszewicz E
Department of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel.
Lancet; 1(8377):593-5 1984

The oncogene *abl*, which resides on chromosome 9, is translocated to chromosome 22 as part of the Philadelphia (Ph⁺) chromosome. Leukaemic cells from 5 of 6 patients with chronic myelogenous leukaemia (CML) and the Ph⁺ chromosome were found to contain a new 8 kb *abl* RNA transcript. This finding raises the possibility that the *abl* oncogene is directly involved in the development of CML. It is suggested that the *abl* gene's expression is altered by the DNA rearrangement in the translocation.

163. LOCALIZATION OF THE CELLULAR ONCOGENES ABL, SIS, AND FES ON HUMAN GERM-LINE CHROMOSOMES

Jhanwar SC, Neil BG, Hayward WS, Chaganti RS
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Cytogenet Cell Genet; 38(1):73-5 1984

The human germ-line positions of the oncogenes *ABL*, *SIS*, and *FES*, the cellular counterparts of the *v-onc* genes of Abelson murine leukemia virus, simian sarcoma virus, and feline sarcoma virus, respectively, have been determined by in situ molecular hybridization of 3H-labeled *v-onc* gene probes to meiotic pachytene chromosomes. The position of *ABL* at 9q34.1 corresponds to the breakpoint in chromosome 9 in the translocation that gives rise to the Philadelphia chromosome, t(9;22)(q34;q11); the position of *SIS* at 22q13.1 is distal to the breakpoint in this chromosome. *FES* at 15q26.1 is also distal to the breakpoint in chromosome 15 in the translocation commonly seen in acute promyelocytic leukemia, t(15;17)(q24;q22).

164. TWO CASES OF VARIANT PHILADELPHIA CHROMOSOME RESULTING FROM TRANSLOCATION (21;22) AND (3;19;22)

Heikkila E, Lin CC, Hoo JJ
Department of Pediatrics, University of Calgary, Canada.
Cancer Genet Cytogenet; 11(2):223-6 1984

Two further cases of variant Philadelphia chromosome are presented. The possible presence of a specific oncogene on the long arm of chromosome 9 is discussed.

165. AN ALTERATION OF THE HUMAN C-ABL PROTEIN IN K562 LEUKEMIA CELLS UNMASKS ASSOCIATED TYROSINE KINASE ACTIVITY

Konopka JB, Watanabe SM, Witte ON
Department of Microbiology, University of California, Los Angeles.
Cell; 37(3):1035-42 1984

The *v-abl* protein is known to be a tyrosine-specific protein kinase. However, its normal cellular homolog, *c-abl* P150, is not detectably phosphorylated on tyrosine in vivo or in vitro. The lack of associated tyrosine kinase activity for the *c-abl* protein seems paradoxical since it is the *c-abl*-derived sequences of the *v-abl* protein that encode the kinase activity. We have detected an altered human *c-abl* protein (P210) with associated tyrosine kinase activity in the K562 leukemia cell line. K562 cells are known to have a 9:22 chromosomal translocation involving the *c-abl* locus and have amplified the

c-abl gene 4 to 8 fold. The altered P210 human *c-abl* is serologically and structurally related to the normal *c-abl* protein. A structural alteration of the human *c-abl* protein. K562 cells may have unmasked its associated tyrosine kinase activity. This altered *c-abl* protein may have important implications for a mechanism of activation of this oncogene.

166. REARRANGEMENT AND AMPLIFICATION OF C-ABL SEQUENCES IN THE HUMAN CHRONIC MYELOGENOUS LEUKEMIA CELL LINE K-562

Collins SJ, Groudine MT
Department of Medicine, Veterans Administration Medical Center, Seattle, Washington.
Proc Natl Acad Sci USA; 80(15):4813-7 1983

Structural rearrangements of specific cellular sequences (*c-onc* genes) homologous to acute transforming retrovirus oncogenes (*v-onc* genes) have been recently described in various malignancies. Here we show that human cellular sequences (*c-abl*) homologous to the transforming sequences of the mouse Abelson leukemia virus (*v-abl*) are amplified some 4- to 8-fold in K-562, a Philadelphia chromosome-positive cell line derived from a patient with chronic myelogenous leukemia in blast crisis. Restriction analysis of K-562 and other human DNA samples reveals a significant rearrangement of the *c-abl* sequences in this cell line. In addition, investigation of *v-abl*-related cytoplasmic RNA reveals relatively high levels of these sequences in K-562 compared to other normal and leukemia cells. We have also observed that lambda light chain constant region immunoglobulin genes are amplified in K-562, whereas kappa light chain sequences exhibit no amplification. These results are discussed within the context of the possibility that these Philadelphia chromosome-positive cells exhibit a reciprocal translocation involving chromosome 9 (containing *c-abl*) and chromosome 22 (containing the lambda light chain genes).

167. AMPLIFIED C LAMBDA AND C-ABL GENES ARE ON THE SAME MARKER CHROMOSOME IN K562 LEUKEMIA CELLS

Selden JR, Emanuel BS, Wang E, Cannizzaro L, Palumbo A, Erikson J, Nowell PC, Rovera G, Croce CM
Wistar Institute of Anatomy and Biology, Philadelphia, PA.
Proc Natl Acad Sci USA; 80(23):7289-92 1983

The human leukemia cell line K562, derived from a patient with Philadelphia chromosome-positive chronic myelogenous leukemia, contains amplified *c-abl* oncogenes and unrearranged C lambda genes. Using in situ hybridization techniques, we have determined that the amplified *c-abl* and C lambda DNA sequences of K562 cells are both located on the same abnormal acrocentric marker chromosome, which may represent an altered Philadelphia chromosome.

168. TRANSLOCATION OF C-ABL ONCOGENE CORRELATES WITH THE PRESENCE OF A PHILADELPHIA CHROMOSOME IN CHRONIC MYELOCYTIC LEUKAEMIA

Bartram CR, de Klein A, Hagemeijer A, van Agtoven T, Grunts van Kessel A, Bootsma D, Gravel G, Ferguson-Smith MA, Davies T, Stone M, et al
Department of Cell Biology and Genetics, Erasmus University, Rotterdam, The Netherlands.
Nature; 306(5940):277-80 1983

The localization of cellular oncogenes near the break points of tumour-specific chromosomal aberrations suggests an involvement of these genes in the generation of neoplasms. Recently, we demonstrated the translocation of the human cellular homologue (*c-abl*) of the transforming sequence of Abelson murine leukaemia virus (A-MuLV) from chromosome 9 to the Philadelphia chromosome (Ph⁺) in chronic

myelocytic leukaemia (CML). In an attempt to investigate the significance of this translocation in the pathogenesis of CML, we have now studied two CML patients with complex translocations, t(9; 11; 22) and t(1; 9; 22), and two CML Ph1-negative patients with apparently normal karyotypes. In addition to using blot hybridization with human c-abl probes and DNA from rodent CML cell hybrids as before, we have used in situ hybridization of these probes directly to metaphase chromosomes of CML patients. These studies show that the c-abl gene is translocated in Ph1-positive but not in Ph1-negative CML patients. CML without the Ph1 chromosome seems to be a distinct entity with a different origin, and this view is supported by clinical observations including correlations which reveal a poorer prognosis.

169. LOCALIZATION OF THE C-ABL ONCOGENE ADJACENT TO A TRANSLOCATION BREAK POINT IN CHRONIC MYELOCYTIC LEUKAEMIA

Heisterkamp N, Stephenson JR, Groffen J, Hansen PF, de Klein A, Bartram CR, Grosfeld G
Laboratory of Viral Carcinogenesis, National Cancer Institute-FCRF, Frederick, Maryland.
Nature; 306(5940):239-42 1983

The human c-abl oncogene maps within the region (q34-qter) of chromosome 9 which is translocated to chromosome 22, the Philadelphia (Ph') chromosome, in chronic myelocytic leukaemia (CML). The position of the Ph' chromosomal break point is shown to be variable and, in one CML patient, has been localized immediately 5' of, or within, the c-abl oncogene. A DNA restriction fragment corresponding to this site has been molecularly cloned and shown to represent a chimaeric fragment of DNA from chromosomes 9 and 22.

170. THE BREAKPOINT OF THE PHILADELPHIA CHROMOSOME 22 IN CHRONIC MYELOID LEUKAEMIA IS DISTAL TO THE IMMUNOGLOBULIN LAMBDA LIGHT CHAIN CONSTANT REGION GENES

Rabbitts TH, Forster A, Matthews JG
Laboratory of Molecular Biology, Medical Research Council Centre, Cambridge, England.
Mol Biol Med; 1(1):11-9 1983

Somatic cell hybrids containing chromosomes from a patient with chronic myeloid leukaemia were used as a source of DNA for filter hybridizations with immunoglobulin lambda light chain constant region and c-onc probes. The results show that at least part of the human lambda constant region locus remains on the abnormal chromosome 22 (the Philadelphia chromosome) and therefore that this translocation occurs distal to these genes. Further, in the patient studied the c-abl gene has been translocated to the abnormal chromosome 22, thus creating a new genetic linkage between C lambda and c-abl genes.

171. A CELLULAR ONCOGENE IS TRANSLOCATED TO THE PHILADELPHIA CHROMOSOME IN CHRONIC MYELOCYTIC LEUKAEMIA

de Klein A, Van Kessel AG, Grosfeld G, Bartram CR, Hagemeijer A, Bootsma D, Spurr NK, Heisterkamp N, Groffen J, Stephenson JR
Dept. Cell Biology and Genetics, Erasmus Univ., PO Box 1738, 3000 DR Rotterdam, The Netherlands
Nature; 300(5894):765-767 1982

Involvement of the human cellular homologue (c-abl) of the transforming sequence of Abelson murine leukemia virus (A-MuLV) in the Philadelphia translocation, t(9;22) (q34,q11) was examined. By Southern ink blot analysis of a series of somatic cell hybrids, the human c-abl gene has been localized on chromosome 9. The Philadelphia translocation, involving chromosomes 9 and 22 has been associated with the development of chronic myelocytic leukemia (CML). Using c-abl and

v-abl hybridization probes on blots of somatic cell hybrids, positive hybridization was found when the 22q- (the Philadelphia chromosome), and not the 9q+ derivative of the translocation was present in the cell hybrids. From this, it was concluded in CML, c-abl sequences are translocated from chromosome 9 to chromosome 22q-. This finding is a direct demonstration of a reciprocal exchange between the two chromosomes and suggests a role for the c-abl gene in the generation of CML. (28 Refs)

2.

Reviews of Abl Translocations

172. THE PHILADELPHIA CHROMOSOME: A MODEL OF CANCER AND MOLECULAR CYTOGENETICS

Sandberg AA, Gemmill RM, Hecht Bk, Hecht F
Genetics Center, Southwest Biomedical Research Institute, Tempe, AZ.
Cancer Genes Cytogenet; 21(2):129-46 1986

Recent developments in molecular biology related to the Ph chromosome lead us to an evaluation of knowledge regarding this chromosome. The molecular advances are related to two cellular oncogenes, c-abl and c-sis, and also to the identification and molecular cloning of specific areas of DNA (e.g., band 22q11), permitting the isolation of a probe specific for the translocation breakpoint domain. In the preponderant number of cases examined, it was found that the breakpoints at 22q11 occur within a limited region of up to 5-6 kb, for which the term 'breakpoint cluster region' (bcr) has been suggested. In contrast, breaks at 9q34 seem to occur within a much larger region at the molecular level. Yet to be established is the exact genetic composition of the bcr and a determination as to whether or not the breaks leading to the disease occur preferentially within specific areas. In spite of this level of knowledge, we do not understand how the Ph chromosome participates in CML. If Ph-positive CML is ultimately associated with a cascade of gene activations, the unraveling of their nature and chronology will undoubtedly tell us much of their contribution to the biology of CML, in particular, and to neoplasia, in general. In this respect, the rather clear description of CML in cytogenetic, clinical, and laboratory terms, the relatively long chronic phase of the disease, and the association of the blastic phase with nonrandom chromosome changes (at least in the initial phases of the disease) make Ph-positive CML an excellent candidate for a model for the study of molecular events in human neoplasia. (92 Refs)

173. ACTIVATION OF THE ABL ONCOGENE IN MURINE AND HUMAN LEUKEMIAS (181 Refs)

Konopka JB, Witte ON
Department of Microbiology, University of California, Los Angeles 90024.
Biochim Biophys Acta; 823(1):1-17 1985

Keywords (MeSH): Amino Acid Sequence; Animal; Base Sequence; Cell Transformation, Neoplastic; Human; Leukemia/*familial and genetic; Leukemia, Myelocytic/familial and genetic; Mice; Mouse Leukemia Viruses/genetics; Myristic Acids/metabolism; *Oncogenes; Phosphorylation; Protein Kinases/analysis; Review; RNA, Messenger/analysis; Transduction, Genetic; Translocation (Genetics); Viral Proteins/analysis.

174. CHRONIC MYELOGENOUS LEUKEMIA

Grignani F
Department of Medicine, University of Perugia, Italy.
CRC Crit Rev Oncol Hematol; 4(1):31-66 1985

Chronic myelocytic leukemia (CML) is a well-known myeloproliferative disorder, with typical clinical and hematological features, which develops into a lethal blastic crisis within an average of 4 years. In the last few years much has been learned about the cell responsible for the leukemic deviation, chromosomal abnormalities both in chronic phase and in blastic transformation, biochemical and cytochemical behavior of leukemic cells, and the immunology of the disease. On the contrary, polychemotherapy has brought but little progress in CML treatment. However, thorough research on prognostic factors at the onset of the disorder allows a more rational approach to the treatment, and in the near future interesting progress in bone marrow transplantation is to be expected. Also, monoclonal antibody techniques will reveal further knowledge on the origin and differentiation of leukemic cells and the relationship between the chronic phase and the blastic deviation. (185 Refs)

175. THE RELATION OF ONCOGENESIS AND CYTOGENETICS IN LEUKEMIA AND LYMPHOMA

Pearson M, Rowley JD
Department of Medicine, University of Chicago, Illinois 60637.
Annu Rev Med; 36:471-83 1985

Recent advances in both molecular biology and cancer cytogenetics have provided valuable tools for the study of human oncogenesis. Cellular homologues of viral transforming genes (oncogenes) have been mapped to precise sites on human chromosomes, many of which are involved in specific chromosome translocations in human malignant diseases. Moreover, specific chromosome abnormalities, such as the Ph 1 chromosome, have diagnostic implications. Sufficient data are now available for both acute myeloid and lymphoid leukemia so that the patient's response to therapy and survival can be correlated with the karyotype; it was also shown that the karyotype of the leukemic cells provides significant independent prognostic information. This review summarizes the specific translocations of human leukemias and lymphomas, their clinical implications, and the cellular oncogenes associated with them. Possible mechanisms of oncogenesis and future areas of investigation are also discussed. (42 Refs)

176. THE PHILADELPHIA CHROMOSOME, 25 YEARS LATER, 1960-1985

Hagemeijer A
Nouv Rev Fr Hematol; 27(3):153-5 1985

Keywords (MeSH): Animal; Chromosome Banding; *Chromosomes, Human, 21-22; Chromosomes, Human, 6-12; DNA, Recombinant; Historical Article; History of Medicine, 20th Cent.; Human; Hybrid Cells/ultrastructure; Karyotyping; Leukemia, Myelocytic/*familial and genetic; Nucleic Acid Hybridization; Recombination, Genetic; RNA, Messenger/genetics; Transcription, Genetic; Translocation (Genetics).

177. THE MOLECULAR BIOLOGY OF CHRONIC MYELOGENOUS LEUKAEMIA (77 Refs)

Gale RP, Cannani E
Department of Medicine, Hematology and Oncology, UCLA School of Medicine 90024.
Br J Haematol; 60(3):305-408 1985

Keywords (MeSH): Animal; Chromosome Abnormalities/familial and genetic; Chromosomes, Human, 21-22/ultrastructure; Chromosomes, Human, 6-12/ultrastructure; Human; Leukemia, Myelocytic/*familial and genetic; Mice; Models, Genetic; Models, Molecular; Oncogenes; Review; Transcription, Genetic; Transformation, Genetic; Translocation (Genetics).

tion, Genetic; Transformation, Genetic; Translocation (Genetics).

178. ACTIVATION OF PROTO-ONCOGENES IN HUMAN LEUKEMIAS (40 Refs)

Bartram CR
Department of Pediatrics II, Ulm, Federal Republic of Germany
Blut; 51(2):63-71 1985

Keywords (MeSH): Chromosome Abnormalities/familial and genetic; Chromosome Mapping; Chromosomes, Human, 21-22; Gene Expression Regulation; Human; Leukemia/*familial and genetic; Leukemia, Lymphoblastic/familial and genetic; Leukemia, Myelocytic/familial and genetic; *Oncogenes; Review.

179. THE SIGNIFICANCE OF CHROMOSOME CHANGE TO NEOPLASTIC DEVELOPMENT

Chaganti RS
Lab. of Cancer Genetics and Cytogenetics, Dept. of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021
Chromosome Mutation and Neoplasia. German J, ed. New York, Alan R. Liss, Inc., p. 359-96, 1983.

As historical background, it is noted that von Hanseemann in 1890 suggested that mitotic irregularities were responsible for disordered growth; that Boveri's hypothesis of the origin of neoplasia in mitotic errors drew attention to the importance of somatic cell genotypes; that the stem-line concept of tumor evolution, proposed by Winge and elaborated by the cytological studies of transplanted rodent tumors by Levan, Hauschka, and others, established the importance of selection in the evolution of cell types in a population of proliferating tumor cells that are genotypically heterogeneous; and that the discovery by Nowell and Hungerford of the first specific chromosome abnormality in a human tumor, namely, the Philadelphia chromosome in chronic myelogenous leukemia cells, laid the foundation for the view that tumors are clonal in nature. The next series of major advances in cancer cytogenetics came about in the early 1970s and coincided with the introduction of new methods of study such as banding analysis of chromosomes and somatic cell hybridization. In the present article, the role of chromosome change in the origin and evolution of neoplastic cells is reviewed under the following section headings and subheadings: chromosome changes in neoplastic cells (specificity of chromosome changes in human neoplasia; inducing agent-specific chromosome changes; target-cell-specific chromosome changes; the question of normal karyotypes in tumor cells), genetic analysis of neoplastic proliferation by somatic cell hybridization, and the chromosome-breakage syndromes (the neoplasms; neoplasia-associated traits). The neoplasia-associated traits that are considered consist of immunodeficiency, clonal proliferation, developmental defects, carcinogen sensitivity, and somatic mutation. (193 Refs)

C.

TRANSLOCATIONS INVOLVING OTHER ONCOGENES

1.

Translocations Near or Involving the *Sis* Oncogene

180. RAPID INDUCTION OF CARCINOMAS AND GAMMA-GLUTAMYL TRANSPEPTIDASE-RICH CLONES IN N-METHYL-N-BENZYLNITROSAMINE-TREATED HAMSTER BUCCAL POUCH

Solt DB, Calderon-Solt L, Odajima T
Department of Pathology, Northwestern University Medical School,
Chicago, IL.

JNCI; 74(2):437-45 1985

Topical application of N-methyl-N-benzyl nitrosamine [(MBN) CAS: 937-40-6] to Syrian hamster buccal pouch epithelia resulted within 4 days in the induction of epithelial cell foci with histochemical gamma-glutamyl transpeptidase (GGTase) activity. Approximately 94% of the foci consisted of individual cells or nests of 3 cells or less, as visualized in whole mounts of GGTase-stained pouch epithelia. During a regimen of twice weekly MBN applications, the GGTase-stained foci increased in size to a maximum diameter of approximately 0.4 mm by the third week. In histologic sections, the enlarging foci were similar morphologically to those of the adjacent GGTase-negative epithelium. Groups of animals treated with MBN for 2, 4, and 8 weeks developed a buccal pouch tumor incidence of 43, 86, and 100%, respectively, within 39 weeks or less. Of the 138 papillomas and carcinomas examined, 11 contained patchy GGTase activity.

181. CHROMOSOME TRANSLOCATION T(14;22) AND ONCOGENE (C-SIS) VARIANT IN A PEDIGREE WITH FAMILIAL MENINGIOMA

Bolger GB, Stamberg J, Kirsch IR, Hollis GF, Schwarcz DF, Thomas GH

Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

N Engl J Med; 312(9):564-7 1985

Keywords (MeSH): Aged; Case Report; *Chromosomes, Human, 13-15; *Chromosomes, Human, 21-22; DNA analysis; Female; Human; Karyotyping; Male; Meningeal Neoplasms/*familial and genetic; Meningioma/*familial and genetic; Middle Age; *Oncogenes; Pedigree; Polymorphism (Genetics); *Translocation (Genetics); *Variation (Genetics).

182. LOCALIZATION OF THE HUMAN C-SIS ONCOGENE IN PH1-POSITIVE AND PH1-NEGATIVE CHRONIC MYELOCYTIC LEUKEMIA BY IN SITU HYBRIDIZATION

Bartram CR, de Klein A, Hagemeijer A, Grossfeld G, Heisterkamp N, Groffen J

Department of Cell Biology and Genetics, Erasmus University, Rotterdam, The Netherlands

Blood; 63(1):223-5 1984

Oncogenes are a group of evolutionary conserved cellular genes (c-onc) homologous to the transforming genes of oncogenic retroviruses (v-onc). Some of them are localized near the breakpoints of specific chromosomal aberrations occurring in various neoplasms, as for example the Philadelphia translocation, t(9;22)(q34;q11), in chronic myelocytic leukemia (CML). Recently, we localized the human c-abl oncogene to chromosome region 9q34 and demonstrated a translocation of this gene to the Philadelphia chromosome (Ph1,22q-) in various forms of Ph1-positive, but not Ph1-negative, chronic myelocytic leukemia (CML). Another human oncogene, c-sis, is located on chromosome 22 and was recently reported to be transferred to chromosome 9q+ in one CML patient. We have now studied 2 CML patients with classic and variant types of Ph1 translocation, one Ph1-negative case, and a healthy control using in situ hybridization of a c-sis probe to metaphase chromosomes. These studies show that c-sis: (1) is localized to region 22q12.3-q13.1, far away from the breakpoint region 22q11 in CML, (2) segregates

with the translocated part of chromosome 22 to different chromosomes in Ph1-positive patients, and (3) remains on chromosome 22 in the Ph1-negative case. Therefore, these data give no support for an active role of the c-sis gene in the generation of CML. Thus, if either of these two oncogenes is involved in the development of Ph1-positive CML, c-abl appears to be the more important one.

183. CHRONIC MYELOID LEUKAEMIA AND THE PHILADELPHIA TRANSLOCATION: DO THE C-SIS ONCOGENE AND PLATELET-DERIVED GROWTH FACTOR PROVIDE THE LINK?

Francis GE, Michalevitz R, Wickremasinghe RG

Department of Haematology, Royal Free Hospital, London, U.K.

Leuk Res; 7(6):817-20 1983

The study of cellular oncogenes and of chromosomal abnormalities in human tumours has, in several instances, suggested a link between a specific oncogene translocation and oncogenesis. It was recently suggested that the translocation of the c-abl gene (the human cellular homologue of the transforming sequence of Abelson murine leukaemia virus) from chromosome 9 to 22 in Philadelphia translocation, might have a role in the generation of chronic myeloid leukaemia (CML). We propose an alternative hypothesis and suggest that the translocation of another gene, c-sis, may be more important.

184. CHROMOSOMAL TRANSLOCATION (11; 22) IN CELL LINES OF EWING'S SARCOMA

Turc-Carel C, Philip I, Berger MP, Philip T, Lenoir G

Laboratoire de Cytogenetique, Faculte de Medecine, Dijon.

C R Seances Acad Sci III; 296(23):1101-3 1983

Chromosome studies were performed on 5 Ewing sarcoma cell lines. An identical reciprocal translocation t(11; 22)(q24; q12) was found in 4 cell lines established from 3 different tumors. These results, associated with those obtained at the same time and independently from fresh tumor cells, suggest that the translocation t(11; 22)(q24; q12) may be a chromosomal marker characteristic of Ewing sarcoma cells. This translocation involves the chromosome 22 on which the H-cis oncogene has been located; it could be used as a new tool for exploring the role of genetic transposition in the malignant cell transformation.

185. TRANSLOCATION OF CHROMOSOME 22 IN EWING'S SARCOMA

Aurias A, Rimbaud C, Buffe D, Duboussat J, Mazabraud A

Institut de Progenese, Paris.

C R Seances Acad Sci III; 296(23):1105-7 1983

The chromosomal analysis of four fresh Ewing tumours shows a translocation of the band q12 of the chromosome 22 in all the clones observed. This translocation seems to preferentially involve the band q24 of the chromosome 11. These results are in favour of a consistent translocation in Ewing's sarcoma, and are to be compared with the results obtained in other malignancies. A relation between this translocation and the location of the human oncogene c-sis on the chromosome 22 should be considered.

186. MAPPING OF THE C-SIS ONCOGENE ON HUMAN CHROMOSOME 22 WITH RESPECT TO THE BREAKPOINT ASSOCIATED WITH CHRONIC MYELOID LEUKAEMIA

Goyms MH

Beatson Institute for Cancer Research, Glasgow, U.K.

BioSci Rep; 3(12):1107-11 1983

Chronic myeloid leukaemia (CML) cells are often characterized by the presence of a small chromosome 22, in which

most of the q arm has been translocated to chromosome 9. Using cell hybrids containing different parts of chromosome 22 I have mapped the c-sis oncogene, which is known to be situated on chromosome 22, to a region distal to the CML breakpoint (22q112) and proximal to 22q13. This demonstrates that c-sis is translocated to chromosome 9 in CML cells.

187. GENETIC MAPPING OF THE MOUSE PROTO-ONCOGENE C-SIS TO CHROMOSOME 15

Kozak CA, Sears JF, Hoggan MD
Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland.
Science; 221(4613):867-9 1983

The mouse homolog (c-sis) of the transforming gene of the simian sarcoma virus was mapped to chromosome 15 by the Southern blot analysis of DNA's from hamster-mouse somatic cell hybrids. Alterations in c-sis expression may thus play a role in the various murine neoplastic diseases characterized by rearrangements or duplications of chromosome 15.

188. CHROMOSOMAL LOCALIZATION OF THE HUMAN HOMOLOG (C-SIS) OF THE SIMIAN SARCOMA VIRUS ONC GENE

Dalla Favera R, Gallo RC, Giallango A, Croce CM
Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20205
Science; 218(4573):686-688 1982

Nonrandom chromosome rearrangements of chromosome 22 have been identified in different human malignancies. As a result of Southern blot hybridization of a c-sis probe to DNA's from mouse-human somatic cell hybrids, the human homolog (c-sis) of the transforming gene of simian sarcoma virus was assigned to chromosome 22. Hybrids between thymidine kinase-deficient mouse cells and human fibroblasts carrying a translocation of the region q11-qter of chromosome 22 to chromosome 17 were also analyzed. These studies demonstrate that the human c-sis gene is on region 22q11 greater than qter. (Author abstract) (28 Refs)

2.

Translocations Near or Involving Ras Oncogenes

189. CHROMOSOMAL LOCALIZATION OF THREE HUMAN RAS GENES BY IN SITU MOLECULAR HYBRIDIZATION

Papescu NC, Amisbaugh SC, DiPaolo JA, Tronick SR, Aaronson SA, Swan DC
Laboratory of Biology, National Cancer Institute, Bethesda, Maryland 20205.
Somatic Cell Mol Genet; 11(2):149-55 1985

Three human ras family protooncogenes, c-Ki-ras-1, and c-Ki-ras-2, and N-ras, have been mapped to chromosome bands 6p11-12, 12p11.1-12.1, and 1p11-13, respectively by in situ molecular hybridization. Certain human cancers display consistent and specific alterations involving chromosomes 1, 6, and 12. The precise chromosomal localization of ras genes will permit evaluation of the possible effect of these chromosomal changes on the structure and activities of ras protooncogenes in human neoplasia.

190. CYTOGENETIC STUDY OF TEN CARCINOMAS OF THE BLADDER: INVOLVEMENT OF CHROMOSOMES 1 AND 11

Atkin NB, Baker MC
Department of Cancer Research, Mount Vernon Hospital, Northwood, Middlesex, U.K.
Cancer Genet Cytogenet; 15(3-4):253-68 1985

In direct preparations of ten untreated transitional cell carcinomas of the bladder, chromosomes and were most frequently involved in structural changes (in at least seven tumors each). Three tumors had one or two 11p- chromosomes, and, in other tumors, chromosome had taken part in translocations or isochromosome formation, which, except in one tumor, resulted in a loss of short arm material. Also, there was a tendency for the presence of fewer than expected normal chromosomes. Chromosome anomalies are common in most types of tumor; however, chromosome abnormalities, particularly the loss of short arm material, are not common and may thus characterize carcinoma of the bladder, a finding that is of interest in view of the location of an oncogene, c-Ha-ras1, on 11p. Translocations probably involved chromosome in four tumors. Structurally changed chromosomes were seen in four tumors, including one or two 3q- chromosomes in two or possibly three tumors.

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191. COMPARATIVE ANALYSIS OF MOUSE-HUMAN HYBRIDS WITH REARRANGED CHROMOSOMES 1 BY IN SITU HYBRIDIZATION AND SOUTHERN BLOTTING: HIGH-RESOLUTION MAPPING OF NRAS, NGFB, AND AMY ON HUMAN CHROMOSOME 1

Munkit M, Lindgren V, de Martinville B, Francke U
Department of Human Genetics, Yale University School of Medicine, New Haven, Connecticut.
Somatic Cell Mol Genet; 10(6):589-99 1984

The human protooncogene NRAS and the genes for the beta-subunit of nerve growth factor (NGFB) and for amylase (AMY) have previously been assigned to the proximal short arm of chromosome 1, but their precise positions have not been unequivocally established. By in situ hybridization of DNA probes for the three genes, we have ascertained the location of complementary sequences in mouse-human somatic cell hybrids that contained translocations of chromosome 1. The results agreed with the presence or absence of the human sequences as determined by Southern blotting of hybrid cell DNA. The in situ data confirmed that the genes were present on the cytologically recognized rearranged chromosome. Compared to the autoradiographic silver grain distribution on normal human chromosome 1, our in situ results obtained with the translocation chromosomes allowed much greater precision of mapping. Both NRAS and NGFB map to band 1p22, and AMY was confirmed in band 1p21.

192. REGIONAL CHROMOSOMAL LOCALIZATION OF N-RAS, K-RAS-1, K-RAS-2 AND MYB ONCOGENES IN HUMAN CELLS

McBride OW, Swan DC, Tronick SR, Gel R, Klimanis D, Moore DE, Aaronson SA
Laboratory of Biochemistry, National Cancer Institute, Bethesda, MD.
Nucleic Acids Res; 11(23):8221-36 1983

The identification of transforming genes in human tumor cells has been made possible by DNA mediated gene transfer techniques. To date, it has been possible to show that most of these transforming genes are activated cellular analogues of the ras oncogene family. To better understand the relationship between these oncogenes and other human genes, we have determined their chromosomal localization by analyzing human rodent somatic cell hybrids with molecularly cloned human proto-oncogene probes. It was possible to assign N-ras to chromosome 1 and regionally localize c-Ki-ras-1 and c-Ki-ras-2 to human chromosomes 6pter-q13 and 12q, respectively. These results along with previous studies demonstrate the highly dispersed nature of ras genes in the human genome. Previous reports indicated that the c-myc gene also resides on chromosome 6. It has been possible to sublocalize c-myc to the long arm of chromosome 6 (q15-q21). The non-random aberrations in chromosomes 1, 6 and

12 that occur in certain human tumors suggest possible etiologic involvement of ras and/or myb oncogenes in such tumors.

193. LOCALIZATION OF C-RAS ONCOGENE FAMILY ON HUMAN GERM-LINE CHROMOSOMES

Jhanwar SC, Neel BG, Hayward WS, Chaganti RS
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Proc Natl Acad Sci USA; 80(15):4794-7 1983

The c-ras family is a set of c-onc genes that are highly conserved in vertebrates. The genes in this family are homologous to the transforming genes of Harvey and Kirsten murine sarcoma viruses (v-Ha-ras and v-Ki-ras, respectively). Using an *in situ* molecular hybridization method, we detected three sites on the human pachytene chromosomes that exhibited significant hybridization to v-Ki-ras and v-Ha-ras probes. These were chromomere positions that corresponded to bands 11p14.1, 12p12.1, and 12q24.2 of somatic chromosomes. The relationship between these chromosomal sites and previously defined members of the human c-ras gene family is discussed. These chromosomal sites are known to be involved in specific chromosome changes in a variety of tumors and in several congenital disorders that predispose to neoplastic disease.

194. ONCOGENE FROM HUMAN EJ BLADDER CARCINOMA IS LOCATED ON THE SHORT ARM OF CHROMOSOME 11

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Science; 219(4584):498-501 1983

Chromosomal location of the normal sequences homologous to the transforming gene of the EJ bladder carcinoma cell line were studied using Southern blot analysis to examine 24 different human/rodent-hybrid cell lines derived from fusions between established Chinese hamster or mouse cell lines and normal diploid human fibroblasts or WBC. Hybrids were scored for the presence of the major fragment or the polymorphic alleles. Sequences homologous to the bladder carcinoma transforming gene segregated only with human chromosome 11. Regional localization was accomplished with a subset of 14 somatic cell hybrids, of which 8 contained only part of chromosome 11. Further regional mapping information was obtained from series XXI hybrids in which the human donor carried a balanced reciprocal translocation t(11;15)(p11;p12); the two human chromosomes 11 are morphologically distinguishable, one being normal and the other being distributed between the two products of reciprocal translocation. All results taken together indicate that the cellular homologous sequences are on the short arm of chromosome 11 (region p11 to p15). The oncogene of this bladder carcinoma is homologous to the v-Ha-ras oncogene of Harvey murine sarcoma virus. The 11p11 to p15 region also contains lactate dehydrogenase, A isozyme, the non-alpha-globin gene complex, a locus for catalase, and several loci for cell-surface antigens, as well as several loci related to cell growth or malignancy, including the structural gene for insulin. (31 Refs)

3.

Translocations Near or Involving the Mos Oncogene

195. THE ROLE OF THE C-MOS GENE IN THE 8;21 TRANSLOCATION IN HUMAN ACUTE MYELOBLASTIC LEUKEMIA

Diaz MO, Le Beau MM, Rowley JD, Drabkin HA, Patterson D
Department of Medicine, Pritzker School of Medicine, University of Chicago, Illinois 60637.
Science; 229(4715):767-9 1985

The human c-mos proto-oncogene is located on chromosome 8 at band q22, close to the breakpoint in the t(8;21)(q22;q22) chromosome rearrangement. This translocation is associated with acute myeloblastic leukemia, subgroup M2. The c-myc gene, another proto-oncogene, has been mapped to 8q24. The breakpoint at 8q22 separates these genes, as determined by *in situ* hybridization of c-mos and c-myc probes. The c-mos gene remains on the 8q-chromosome and the c-myc gene is translocated to the 21q+ chromosome. Southern blot analysis of DNA from bone marrow cells of four patients with this translocation showed no rearrangement of c-mos.

196. ISOLATION AND ANALYSIS OF THE 21Q+ CHROMOSOME IN THE ACUTE MYELOGENOUS LEUKEMIA 8;21 TRANSLOCATION: EVIDENCE THAT C-MOS IS NOT TRANSLOCATED

Drabkin HA, Diaz M, Bradley CM, Le Beau MM, Rowley JD, Patterson D
Eleanor Roosevelt Institute for Cancer Research, Denver, CO.
Proc Natl Acad Sci USA; 82(2):464-8 1985

Acute myelogenous leukemia (AML), subgroup M2, is associated with a nonrandom chromosomal translocation, t(8;21)(q22;q22). The oncogene c-mos also has been localized to the q22 band on chromosome 8. There is also evidence that genes on chromosome 21 may be important in the development of leukemia. To determine whether the c-mos oncogene has been translocated in AML-M2 with this translocation and to isolate DNA sequences and genes from these two chromosomes that may be important in malignancy, we constructed somatic cell hybrids between a Chinese hamster ovary cell (CHO) mutant defective in glycine metabolism and myeloblasts with an 8;21 translocation from a patient with AML. We isolated the 21q+ chromosome of this translocation in a somatic cell hybrid and showed that the c-mos oncogene had not been translocated to chromosome 21, ruling out the possibility that translocation of c-mos to chromosome 21 is necessary for development of AML-M2. In addition, there was no detectable rearrangement of the c-mos locus within a 12.4-kilobase region surrounding the gene, indicating that rearrangement of the coding region of the gene itself or alteration of proximal 5' or 3' flanking sequences is not involved. We used this hybrid to determine whether specific DNA sequences and biochemical markers from chromosomes 8 and 21 had been translocated in this case.

197. HUMAN PROTO-ONCOGENE C-MOS MAPS TO 8Q11

Caubet JF, Mathieu-Mabul D, Bernheim A, Larsen CJ, Berger R
Laboratoire d'Oncologie, Hôpital Saint-Louis, Paris, France.
EMBO J; 4(9):2245-8 1985

The c-mos proto-oncogene is the cellular counterpart of the viral oncogene v-mos isolated from Moloney murine sarcoma virus. The c-mos gene locus has previously been assigned to human chromosome 8. By both *in situ* hybridization and molecular hybridization to sorted chromosome DNA (using a c-mos probe) we have localized the c-mos gene to band 8q11. This regional localization is at variance with the one previously reported at 8q22 and may explain why no rearrangement of c-mos has been found in acute leukaemia with the chromosomal translocation t(8;21)(q22;q22).

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198. IDENTIFICATION IN SEVERAL HUMAN MYELOID LEUKEMIAS OR CELL LINES OF A DNA REARRANGEMENT NEXT TO THE C-MOS 3'-END

Revoltella RP, Park M, Fruscalzo A
Institute of Cell Biology, CNR, Roma, Italy.
FEBS Lett; 189(1):97-101 1985

A characteristic DNA rearrangement, the loss of an EcoRI cleavage site next to the 3'-end of the human c-mos gene, has been found to be frequently present in DNA from transformed hematopoietic cells of the myeloid lineage but not in DNA from either normal or transformed cells of different tissue types. Three established cell lines, respectively a promonocytic line (CM-S) and two precursor granulocytic lines (My/K1 and My/K5), carry the same genome rearrangement, but not fibroblasts obtained from the marrow of the same patients. This DNA rearrangement is maintained in three different hybridomas derived by fusion of CM-S cells with normal human embryo hepatocytes.

199. REARRANGED C-MOS LOCUS IN A MOPC 21 MURINE MYELOMA CELL LINE AND ITS PERSISTENCE IN HYBRIDOMAS

Gattoni-Celli S, Hsiao WL, Weinstein IB
Division of Environmental Sciences, Columbia University, New York, New York.
Nature; 306(5945):793-6 1983

Studies of a number of normal and carcinogen-transformed murine cell lines, and a variety of murine tissues, have indicated that, in contrast to several other cellular oncogenes, the oncogene c-mos gene is usually transcriptionally silent. The recent report by Rechavi et al. indicating that in the mouse myeloma XRPC24 originally induced by pristane (2,6,10,14-tetramethylpentadecane) the c-mos gene is rearranged and transcriptionally active, and that it can transform murine fibroblasts in a transfection assay, is therefore of considerable interest. Here we show that the c-mos locus has undergone a similar rearrangement, and is also transcriptionally active, in the cell line P3-X63-Ag8-653, a derivative of the mouse myeloma MOPC 21 which was induced by mineral oil. This line is widely used for making hybridomas that synthesize monoclonal antibodies. We also demonstrate that the rearranged c-mos sequence is maintained in three different hybridomas derived by fusion of this cell line with normal murine spleen lymphocytes, suggesting that it may play a role in the continuous growth and/or constitutive immunoglobulin production by these hybridomas.

200. HOMOLOGY BETWEEN AN ENDOGENOUS VIRAL LTR AND SEQUENCES INSERTED IN AN ACTIVATED CELLULAR ONCOGENE

Kuff EL, Fornstra A, Lueders K, Rechavi G, Givol D, Canaani E
Laboratory of Biochemistry, National Cancer Institute, Bethesda, Maryland.
Nature; 302(5908):347-8 1983

Recently, some of us reported the detection and molecular cloning of a rearranged cellular oncogene, designated rc-mos, from a non-virally-induced mouse myeloma, XRPC24. Recombinant lambda phage DNA containing the rc-mos gene was active in transforming NIH 3T3 cells in a transfection assay, whereas recombinant DNA containing the unrearranged c-mos gene was not. In rc-mos, coding sequences from the 5' end of c-mos were found to have been displaced by a novel cellular element whose nucleotide sequence was reported. We now document the fact that a 349-base pair (bp) segment of the novel DNA immediately adjacent to the retained c-mos sequences in rc-mos has close homology with the long terminal repeat (LTR) of a known intracisternal A-particle gene. This homology was mentioned in Nature re-

cendy after it had been brought to the attention of the editors (N. Hozumi and R. Hawley, personal communication).

201. ACTIVATION OF A CELLULAR ONCOGENE BY DNA REARRANGEMENT: POSSIBLE INVOLVEMENT OF AN IS-LIKE ELEMENT

Rechavi G, Givol D, Canaani E
Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot 76100, Israel.
Nature; 300(5893):607-611 1982

The cellular oncogene c-mos is rearranged in a mouse myeloma and the tumor mRNA contains transcripts hybridizing with a v-mos probe. The rearranged gene (RC-mos) was cloned in gamma phage and shown to transform mouse fibroblasts in transfection assays. RC-mos differs from its progenitor, c-mos, only at the 5' end of the gene, where c-mos sequences have been substituted by a novel cellular DNA fragment. This fragment contains a 139-base pair (bp) insertion sequence (IS)-like element localized immediately 5' to the junction with c-mos. This is the first demonstration in a non-virally-induced tumor of activation of a cellular oncogene by a mechanism possibly involving DNA transposition. (Author abstract) (51 Refs)

4.

Translocations Near or Involving Other Oncogenes

202. IDENTICAL CHROMOSOME TRANSLOCATIONS INVOLVING THE REGION OF THE C-MYB ONCOGENE IN FOUR METASTASES OF A MEDIASTINAL TERATOCARCINOMA

Oosterhuis JW, de Jong B, van Dalen I, van der Meer I, Visser M, de Leij L, Mesander G, Collard JG, Schraffordt Koops H, Sleijfer DT
Department of Pathology, University of Groningen, The Netherlands.
Cancer Genet Cytogenet; 15(1-2):99-107 1985

A 39-year-old white male presented with a disseminated mediastinal teratocarcinoma. Karyotyping was performed on two mature residual metastatic lesions in the lungs immediately following chemotherapy, on a recurring lung lesion after 5 months, and on a metastasis in the right thigh 5 months after salvage chemotherapy. All four lesions were pseudoeuploid and showed identical chromosomal abnormalities: a translocation with the two chromosomes and one chromosome involved, resulting in 46, XY, t(6;11)(q21;q23;q13). The breakpoint in chromosome 11 is in the region to which the oncogene c-myb has been localized, and the breakpoint in chromosome 6 is at a known fragile and possibly oncogenic site, suggesting that the translocations in this case may have played a crucial role in the development of the malignancy.

203. ACTIVATION OF THE C-MYB LOCUS BY VIRAL INSERTIONAL MUTAGENESIS IN PLASMACYTOID LYMPHOSARCOMAS

Sben-Ong GL, Potter M, Mushinski JF, Lavu S, Reddy EP
Laboratory of Genetics, National Cancer Institute, Bethesda, Maryland.
Science; 226(4678):1077-80 1984

Rearrangement in the c-myb locus of each of four independently derived BALB/c plasmacytoid lymphosarcoma (ABPL's) is due to the insertion of a defective Moloney murine leukemia virus (M-MuLV) into a 1.5-kilobase-pair stretch of cellular DNA at the 5' end of the v-myb-related sequences. This retroviral insertion is associated with abnormal transcription of myb sequences and probably represents a step in the neoplastic transformation of ABPL cells.

204. DNA REARRANGEMENT AND ALTERED RNA EXPRESSION OF THE C-MYB ONCOGENE IN MOUSE PLASMACYTOID LYMPHOSARCOMAS

Musbinshi JF, Potter M, Bauer SR, Reddy EP
Laboratory of Genetics, National Cancer Institute, Bethesda,
Maryland.

Science; 220(4599):795-8 1983

Three types of tumors termed plasmacytomas (ABPC's), lymphosarcomas (ABLS's), and plasmacytoid lymphosarcomas (ABPL's) arise in BALB/c mice treated with pristane and Abelson murine leukemia virus (A-MuLV). While most ABPC's and BLS's contain integrated A-MuLV proviral genome and synthesize the v-abl RNA, most ABPL's do not. The ABPL tumors were examined for the expression of other oncogenes that may be associated with their transformed state, in the absence of transforming virus. These tumors expressed abundant c-myb RNA of unusually large size and showed DNA rearrangements of the c-myb locus.

205. CHROMOSOMAL SUBLOCALIZATION OF HUMAN C-MYB AND C-FES CELLULAR ONC GENES

Harper ME, Franchini G, Love J, Simon MI, Gallo RC, Wong-Staal F

Agouron Institute, La Jolla, California.
Nature; 304(5922):169-71 1983

The transforming genes of acutely transforming retroviruses are derived from conserved cellular genes (c-onc genes) which are believed to be important in normal cell growth and differentiation. Recent studies indicate that altered expression of c-onc genes, for example, by insertion of viral genomes, gene amplification or chromosomal translocation, can lead to development of malignant diseases in man and animals. c-myb and c-fes are homologues of the transforming genes of avian myeloblastosis virus and feline sarcoma virus (Gardner and Snyder-Theilen strains), respectively. c-myb is transcribed preferentially in immature haematopoietic cells and probably codes for a protein important in differentiation of these cells. The viral fes gene, like several other viral onc genes, encodes a tyrosine-specific protein kinase. However, c-fes transcripts have not been detected in the types of human cells examined so far. c-myb and c-fes have been assigned to human chromosomes 6 and 15 respectively. Specific aberrations involving these chromosomes have been observed at high frequency in several human neoplasms. We have now sublocalized c-myb to 6q22-24 and c-fes to 15q25-26 by in situ hybridization of the human c-onc probes to human mitotic chromosome preparations. These chromosomal segments are indeed involved in nonrandom translocations in several human tumours. The results encourage further investigation into the role of onc genes in the pathogenesis of specific neoplasms.

206. LOCUS OF THE ALPHA-CHAIN OF THE T-CELL RECEPTOR IS SPLIT BY CHROMOSOME TRANSLOCATION IN T-CELL LEUKEMIAS

Erikson J, Williams DL, Finan J, Nowell PC, Croce CM
Wistar Institute, Philadelphia, Pennsylvania 19104.
Science; 229(4715):784-6 1985

Mouse lymphoma cells were hybridized with two human acute T-cell leukemias with a t(11;14) (p13;q11) translocation and the segregated hybrids were examined for the presence of the DNA segments coding for the constant (C) and the variable (V) regions of the alpha chain (C alpha and V alpha) of the T-cell receptor. The C alpha segment was translocated to the involved chromosome 11 (11p+) while the V alpha segment remained on the involved chromosome 14 (14q-). The data indicate that the locus for the alpha chain of the T-cell receptor is split by the chromosomal breakpoint between the V alpha and the C alpha gene segments, and

that the V alpha segments are proximal to the C alpha segment within chromosome band 14q11.2.

207. GENE FOR ALPHA-CHAIN OF HUMAN T-CELL RECEPTOR: LOCATION ON CHROMOSOME 14 REGION INVOLVED IN T-CELL NEOPLASMS

Croce CM, Isobe M, Palumbo A, Puck J, Ming J, Twardy D, Erikson J, Davis M, Rovera G

Wistar Institute, Philadelphia, Pennsylvania.
Science; 227(4690):1044-7 1983

A human complementary DNA clone specific for the alpha-chain of the T-cell receptor and a panel of rodent X human somatic cell hybrids were used to map the alpha-chain gene to human chromosome 14 in a region proximal to the immunoglobulin heavy chain locus. Analysis by means of in situ hybridization of human metaphase chromosomes served to further localize the alpha-chain gene to region 14q11q12, which is consistently involved in translocations and inversions detectable in human T-cell leukemias and lymphomas. Thus, the locus for the alpha-chain T-cell receptor may participate in oncogene activation in T-cell tumors.

208. BREAKPOINTS IN THE HUMAN T-CELL ANTIGEN RECEPTOR ALPHA-CHAIN LOCUS IN TWO T-CELL LEUKAEMIA PATIENTS WITH CHROMOSOMAL TRANSLOCATIONS

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Nature; 317(6037):344-6 1985

Specific chromosomal translocations have been observed in several human and animal tumours and are believed to be important in tumorigenesis. In many of these translocations the breakpoints lie near cellular homologues of transforming genes, suggesting that tumour development is partly due to the activation of these genes. The best-characterized example of such a translocation occurs in mouse plasmacytoma and human B-cell lymphoma, where c-myc, the cellular homologue of the viral oncogene myc, is brought into close proximity with either the light- or heavy-chain genes of the immunoglobulin loci, resulting in a change in the regulation of the myc gene. T-cell malignancies also have characteristic chromosomal abnormalities, many of which seem to involve the 14q11-14q13 region. This region has recently been found to contain the alpha-chain genes of the human T-cell antigen receptor. Here we determine more precisely the chromosome breakpoints in two patients whose leukaemic T cells contain reciprocal translocations between 11p13 and 14q13. Segregation analysis of somatic cell hybrids demonstrates that in both patients the breakpoints occur between the variable (V) and constant (C) region genes of the T-cell receptor alpha-chain locus, resulting in the translocation of the C-region gene from chromosome 14 to chromosome 11. As the 11p13 locus has been implicated in the development of Wilms' tumour, it is possible that either the Wilms' tumour gene or a yet unidentified gene in this region is involved in tumorigenesis and is altered as a result of its translocation into the T-cell receptor alpha-chain locus.

209. GENES FOR BETA CHAIN OF HUMAN T-CELL ANTIGEN RECEPTOR MAP TO REGIONS OF CHROMOSOMAL REARRANGEMENT IN T CELLS

Morton CC, Duby AD, Eddy RL, Shows TB, Seidman JG
Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115.

Science; 228(4699):582-5 1985

The T-cell antigen receptor is a cell-surface molecule that participates in the immune response. In the present experi-

ments the genes encoding the beta chain of the T-cell receptor were found to reside on the long arm of human chromosome 7 at or near band q32. Related sequences were found on the short arm of chromosome 7 in bands p15-21 in some experiments. Chromosomal rearrangements in T-cells from normal individuals and patients with ataxia telangiectasia have previously been observed at and near these map assignments for the beta-chain genes.

210. LOCATION OF GENE FOR BETA SUBUNIT OF HUMAN T-CELL RECEPTOR AT BAND 7Q35, A REGION PRONE TO REARRANGEMENTS IN T CELLS

Isobe M, Erikson J, Emanuel BS, Nowell PC, Croce CM
Wistar Institute of Anatomy and Biology, Philadelphia,
Pennsylvania 19104.
Science; 228(4699):580-2 1985

The T-cell receptor is formed by two chains, alpha and beta, for which specific clones were recently obtained. In this report the gene for the beta chain of the human T-cell receptor was located on the long arm of chromosome 7, band q35, by means of in situ hybridization. This chromosome region in T cells is unusually prone to develop breaks in vivo, perhaps reflecting instability generated by somatic rearrangement of T-cell receptor genes during normal differentiation in this cell lineage.

211. HU-ETS-1 AND HU-ETS-2 GENES ARE TRANSPOSED IN ACUTE LEUKEMIAS WITH (4;11) AND (8;21) TRANSLOCATIONS

Sacchi N, Watson DK, Guerts van Kessel AH, Hagemeijer A, Kersey J, Drabkin HD, Patterson D, Papas TS
Laboratory of Molecular Oncology, National Cancer Institute,
Frederick, MD 21701.
Science; 231(4736):379-82 1986

Human probes identifying the cellular homologs of the v-ets gene, Hu-ets-1 and Hu-ets-2, and two panels of rodent-human cell hybrids were used to study specific translocations occurring in acute leukemias. The human ets-1 gene was found to translocate from chromosome 11 to 4 in the t(4;11)(q21;q23), a translocation characteristic of a subtype of leukemia that represents the expansion of a myeloid/lymphoid precursor cell. Similarly, the human ets-2 gene was found to translocate from chromosome 21 to chromosome 8 in the t(8;21)(q22;q22), a nonrandom translocation commonly found in patients with acute myeloid leukemia with morphology M2 (AML-M2). Both translocations are associated with expression different from the expression in normal lymphoid cells of ets genes, raising the possibility that these genes play a role in the pathogenesis of these leukemias.

212. THE ETS SEQUENCE FROM THE TRANSFORMING GENE OF AVIAN ERYTHROBLASTOSIS VIRUS, E26, HAS UNIQUE DOMAINS ON HUMAN CHROMOSOMES 11 AND 21: BOTH LOCI ARE TRANSCRIPTIONALLY ACTIVE

Watson DK, McWilliams-Smith MJ, Nunn MF, Duesberg PH, O'Brien SJ, Papas TS
Laboratory of Molecular Oncology, National Cancer Institute,
Frederick, MD 21701.
Proc Natl Acad Sci USA; 82(21):7294-8 1985

Human DNA segments homologous to the ets region from the transforming gene of avian erythroblastosis virus, E26, were molecularly cloned and shown to be closely related to the viral equivalent by hybridization and partial sequence analysis. The transforming gene of E26 has a tripartite origin with the structure delta gag [1.2 kilobases (kb) from the viral gag gene]-myb(0.9 kb from the chicken myb gene)-ets (1.6 kb from the chicken ets gene). Human ets DNA is located on two distinct human chromosomes. The human ets-1 locus on chromosome 11 encodes a single mRNA of 6.8 kb; the

second locus, ets-2 on chromosome 21, encodes three mRNAs of 4.7, 3.2, and 2.7 kb. The ets-related sequences of human DNA on chromosomes 11 and 21 are discontinuous, except for a small overlap region encoding 14 amino acids, where 12 are conserved between these two loci. By contrast, the chicken homolog has contiguous ets-1 and ets-2 sequences and is primarily expressed in normal chicken cells as a single 7.5-kb mRNA. We conclude that the ets sequence shared by the virus, the chicken, and humans is likely to contain at least two dissociable functional domains, ets-1 and ets-2. Thus, the tripartite transforming gene of E26 includes four distinct domains that may be functionally relevant for the transforming function of the virus (delta gag, myb, ets-1, and ets-2).

213. CHROMOSOMAL LOCALIZATION OF THE HUMAN PROTO-ONCOGENE C-ETS

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Nature; 310(5978):581-3 1984

E26 is an acute leukaemia avian retrovirus which induces myeloblastosis and erythroblastosis in vivo and transforms erythroblasts and myeloblasts in vitro. It contains the oncogene v-myb (ref. 4), first described for avian myeloblastosis virus (AMV), as well as a second specific nucleotide sequence, v-ets located 3' to v-myb (refs 5,6). We have reported that v-ets has a cellular counterpart (c-ets) in chicken and human DNA. Now, using two independent methods - hybridization with human c-ets probe of sorted chromosomes and in situ hybridization - we report the localization of the ets locus on human chromosome 11 at bands q23-q24. This finding may be important, as specific breakpoints around this position have been reported for human malignancies such as acute monocytic leukaemia and Ewing's sarcoma.

214. INVOLVEMENT OF THE BCL-2 GENE IN HUMAN FOLLICULAR LYMPHOMA

Tsujimoto Y, Cossman J, Jaffe E, Croce CM
Wistar Institute, Philadelphia, Pennsylvania 19104.
Science; 228(4706):1440-3 1985

Recombinant DNA probes were cloned for the areas flanking the breakpoint on chromosome 18 in cells from a patient with acute lymphocytic leukemia of the B-cell type; cells of this line carry the t(14;18) chromosomal translocation. Two of the probes detected DNA rearrangements in approximately 60 percent of the cases of follicular lymphoma screened. In follicular lymphoma, most of the breakpoints in band q21 of chromosome 18 were clustered within a short stretch of DNA, approximately 2.1 kilobases in length. Chromosome 18-specific DNA probes for the areas flanking the breakpoints also detected RNA transcripts 6 kilobases in length in various cell types. The gene coding for these transcript (the bcl-2 gene) seems to be interrupted in most cases of follicular lymphomas carrying the t(14;18) chromosomal translocation.

215. THE T(14;18) CHROMOSOME TRANSLOCATIONS INVOLVED IN B-CELL NEOPLASMS RESULT FROM MISTAKES IN VDJ JOINING

Tsujimoto Y, Gorham J, Cossman J, Jaffe E, Croce CM
Wistar Institute, Philadelphia, Pennsylvania 19104.
Science; 229(4720):1390-3 1985

In this study, the joining sequences between chromosomes 14 and 18 on the 14q+ chromosomes of a patient with pre-B-cell leukemia and four patients with follicular lymphoma carrying a t(14;18) chromosome translocation were analyzed. In each case, the involved segment of chromosome 18 has re-

combined with the immunoglobulin heavy-chain joining segment (JH) on chromosome 14. The sites of the recombination on chromosome 14 are located close to the 5' end of the involved JH segment, where the diversity (D) regions are rearranged with the JH segments in the production of active heavy-chain genes. As extraneous nucleotides (N regions) were observed at joining sites and specific signal-like sequences were detected on chromosome 18 in close proximity to the breakpoints, it is concluded that the t(14;18) chromosome translocation is the result of a mistake during the process of VDJ joining at the pre-B-cell stage of differentiation. The putative recombinase joins separated DNA segments on two different chromosomes instead of joining separated segments on the same chromosome, causing a t(14;18) chromosome translocation in the involved B cells.

216. CLONING THE CHROMOSOMAL BREAKPOINT OF T(14;18) HUMAN LYMPHOMAS: CLUSTERING AROUND JH ON CHROMOSOME 14 AND NEAR A TRANSCRIPTIONAL UNIT ON 18

Bakshi A, Jensen JP, Goldman P, Wright JJ, McBride OW, Epstein AL, Korsmeyer SJ
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Cell; 41(3):899-906 1985

Specific chromosomal translocations found in distinct neoplasms suggest that genes that flank such breakpoints play a critical role in transformation. We have characterized the t(14;18)(q32;q21) chromosomal translocation present in over 60% of human follicular lymphomas. We exploited an unexpected rearrangement of an Ig heavy-chain gene to clone the chromosomal breakpoint. An element isolated from 18q21 mediated translocations in all four t(14;18) bearing cell lines and in six of 11 follicular lymphomas, but did not normally rearrange in other B or non-B cells. The breakpoints clustered within a small 4.3 kb region on chromosome 18. The breakpoints on chromosome 14 were focused within or immediately 5' to JH. These breakpoints retained the Ig enhancer region close to a new transcriptional unit identified on chromosome segment 18q21. Since none of the cellular oncogenes are known to map to 18q21, cloning this element provides an opportunity to characterize a potentially new transforming gene.

217. NUCLEOTIDE SEQUENCE OF A T(14;18) CHROMOSOMAL BREAKPOINT IN FOLLICULAR LYMPHOMA AND DEMONSTRATION OF A BREAKPOINT-CLUSTER REGION NEAR A TRANSCRIPTIONALLY ACTIVE LOCUS ON CHROMOSOME 18

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Proc Natl Acad Sci USA; 82(21):7439-43 1985

The t(14;18)(q32;q21) chromosomal translocation characteristic of follicular lymphomas is the most common cytogenetic abnormality known to be associated with any specific type of hematolymphoid malignancy. A fragment of DNA containing the crossover point between chromosomes 14 and 18 was cloned from the tumor cells of a patient with a follicular lymphoma carrying this translocation. Nucleotide sequence analysis of the breakpoint DNA revealed that the break in chromosome 14 occurred in joining region 4(J4) of the nonfunctional immunoglobulin heavy chain allele. This finding and other structural similarities of the breakpoint with the functional diversity region-joining region (D-J) joint in this lymphoma suggest that D-J recombination enzymes played a role in the mechanism of the t(14;18) translocation. Hybridization analysis of DNA from 40 follicular lymphomas showed that the majority of t(14;18) translocations occur on chromosome

18 DNA within 4.2 kilobases of the cloned breakpoint. A DNA probe from this breakpoint-cluster region detects transcription products in the tumor cells from which it was cloned and in a B-lymphoma cell line containing a t(14;18) translocation.

218. THE CHROMOSOME 14 BREAKPOINT IN NEOPLASTIC B CELLS WITH THE T(11;14) TRANSLOCATION INVOLVES THE IMMUNOGLOBULIN HEAVY CHAIN LOCUS

Erikson J, Finan J, Tsujimoto Y, Nowell PC, Croce CM
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Proc Natl Acad Sci USA; 81(13):4144-8 1984

We hybridized neoplastic cells from a patient with chronic lymphocytic leukemia of the B-cell type, which carried a reciprocal chromosomal translocation between chromosomes 11 (q13) and 14 (q32) with mouse plasmacytoma cells. The hybrid cells were studied for the presence, rearrangement, and expression of the human immunoglobulin mu chain locus. The results indicate that the expressed mu chain gene is located on the normal chromosome 14, whereas the 14q+ translocation chromosome carries the excluded immunoglobulin constant (C) region mu chain allele (C mu) but does not contain variable (V) region heavy chain genes (VH). Since we found that the heavy chain joining region DNA (JH) of the excluded mu chain gene is on the 14q+ chromosome, we can conclude that the chromosomal break observed in the leukemic cells occurred in a chromosomal region within or 5' of the JH region. With these results, it is logical to postulate that a gene, for which we suggest the name bcl-1, is located on band q13 of chromosome 11 and is activated by its translocation into close proximity with the rearranged heavy chain locus on chromosome 14q+, contributing to the neoplastic transformation of the B cells with the t(11;14) chromosomal translocation.

219. CLUSTERING OF BREAKPOINTS ON CHROMOSOME 11 IN HUMAN B-CELL NEOPLASMS WITH THE T(11;14) CHROMOSOME TRANSLOCATION

Tsujimoto Y, Jaffe E, Cassman J, Gorham J, Nowell PC, Croce CM
Wistar Institute, Philadelphia, Pennsylvania 19104.
Nature; 315(6017):340-3 1985

The t(11;14) (q13;q32) chromosome translocation has been reported in diffuse small and large cell lymphomas and in chronic lymphocytic leukaemia (B-CLL) and multiple myeloma. Because chromosome band 14q32 is involved in this translocation, as well as in the t(8;14) (q24;q32) translocation of the Burkitt tumour, interruption of the immunoglobulin heavy-chain locus was postulated for this rearrangement. We have cloned the chromosomal joinings between chromosomes 11 and 14 and also between chromosomes 14 and 18, in B-cell tumours carrying translocations involving these chromosomes, and suggested the existence of two translocated loci, bcl-1 and bcl-2, normally located on chromosomes 11 (band q13) and 18 (band q21) respectively, involved in the pathogenesis of human B-cell neoplasms. The results indicate that in the leukaemic cells from two different cases of CLL, the breakpoints on chromosome 11 are within 8 nucleotides of each other and on chromosome 14 involve the J4-DNA segment. Because we detected a 7mer-9mer signal-like sequence with a 12-base-long spacer on the normal chromosome 11, close to the breakpoint, we speculate that the t(11;14) chromosome translocation in CLL may be sequence specific and may involve the recombination system for immunoglobulin gene segment (V-D-J) joining.

220. ABNORMALITIES OF CHROMOSOME 14 AT BAND 14Q11 IN JAPANESE PATIENTS WITH ADULT T-CELL LEUKEMIA

Sadamori N, Kusano M, Nishino K, Tagawa M, Yae E, Yamada Y, Amagasaki T, Kinoshita K, Ichimaru M
Department of Hematology, Nagasaki University School of Medicine, Japan.
Cancer Genet Cytogenet; 17(3):279-82 1985

Keywords (MeSH): Adult; Aged; *Chromosome Aberrations; *Chromosomes, Human, 13-15; Female; Human T-Cell Leukemia Virus; Human; Leukemia/*familial and genetic; Male; Middle Age; Retrovirus Infections/*familial and genetic.

221. CYTOGENETIC STUDIES ON PATIENTS WITH CHRONIC T CELL LEUKEMIA/LYMPHOMA

Ueshima Y, Rowley JD, Variakojis D, Winter J, Gordon L
Department of Medicine, University of Chicago, IL.
Blood; 63(5):1028-38 1984

Cytogenetic studies were performed on three patients with chronic T cell leukemia and on one patient with T cell lymphoma. One of the patients had leukemic cells derived from a suppressor T cell clone, another expressed OKT3, 4, and 8, and cells of the other two were derived from a helper T cell clone. All patients had an abnormal karyotype in peripheral blood or bone marrow cultured with or without mitogen. Modal chromosome numbers were 42 and 44/45 in one patient each and 47 in the 2 others. The structural and numerical abnormalities involved almost all chromosomes, except no. 19 and the X chromosome. All patients had a rearrangement of the long arm of no. 14, with a break at band 14q11;3 patients also had a break at 14q32. An inversion of 14q occurred in two patients; a tandem translocation involving both no. 14 chromosomes and a translocation between no. 14 and no. 17 each occurred in one patient. The break in 14q at band q11 in our cases resembles the chromosome change reported in ataxia telangiectasia. This provides added support for the proposal that a 14q rearrangement involving band q11-12, with or without an accompanying break in 14q32, may confer a proliferative advantage on lymphocytes, especially on those of T cell origin.

222. COMMON REGION ON CHROMOSOME 14 IN T-CELL LEUKEMIA AND LYMPHOMA

Hecht F, Morgan R, Hecht BK, Smith SD
Genetics Center and Cancer Research Center, Southwest Biomedical Research Institute, Tempe, Arizona.
Science; 226(4681):1445-7 1984

Chromosome 14 breakpoints in malignant human lymphocytes cluster on the long (q) arm near bands q11 and q32. An inversion of chromosome 14 due to breaks in q11.2 and q32.3 has now been found in a newly established childhood T-cell lymphoma cell line and confirmed in T-cell chronic lymphocytic leukemia. A translocation was also found between chromosomes 10 and 14 with a breakpoint at 14q11.2 in another T-cell lymphoma cell line. It is proposed that a proximal region on chromosome 14 in or near sub-band q11.2 is related to T-cell function. Rearrangements in this region may affect the growth of T lymphocytes and be involved in the development of T-cell malignancies.

223. A 14;18 AND AN 8;14 CHROMOSOME TRANSLOCATION IN A CELL LINE DERIVED FROM AN ACUTE B-CELL LEUKEMIA

Pegoraro L, Palumbo A, Erikson J, Falda M, Giovanazzo B, Emanuel BS, Rovera G, Nowell PC, Croce CM
Istituto di Medicina Interna, University of Turin, Italy.
Proc Natl Acad Sci USA; 81(22):7166-70 1984

We have established a cell line, which we named 380, from a young male with acute lymphoblastic leukemia (FAB type

L2). Karyologic analysis of this cell line indicates that it carries an 8;14 and a 14;18 chromosome translocation, which are characteristic of Burkitt lymphoma and of follicular lymphoma, respectively. This cell line is Epstein-Barr virus antigen-negative, reacts with monoclonal antibodies specific for B cells, and contains rearranged immunoglobulin heavy and light chain genes, but does not express human immunoglobulins. In this cell line, both mu heavy chain constant (C_{mu}) loci are rearranged within the joining (JH) DNA segment. One of the JH segments on one of the 14q+ chromosomes is rearranged with a segment of chromosome 8, where the c-myc oncogene resides, while the other is rearranged with a segment of chromosome 18 where a putative oncogene, which we have called bcl-2, is located. The c-myc oncogene, which is translocated to one of the 14q+ chromosomes, is in its germ-line configuration more than 14 kilobases away from both the JH segment and the heavy chain enhancer that is located between the JH and mu switch region. Based on these findings, we propose a model of some aspects of B-cell oncogenesis according to which B-cell neoplasms carrying translocations involving the heavy chain loci on both human chromosomes 14 are the result of a multiple step process.

224. CLONING OF THE CHROMOSOME BREAKPOINT OF NEOPLASTIC B CELLS WITH THE T(14;18) CHROMOSOME TRANSLOCATION

Tsujimoto Y, Finger LR, Yunis J, Nowell PC, Croce CM
Wistar Institute, Philadelphia, Pennsylvania.
Science; 226(4678):1097-9 1984

From an acute B-cell leukemia cell line, a DNA probe was obtained that was specific for chromosome 18 and flanked the heavy chain joining region of the immunoglobulin heavy chain locus on chromosome 14. This probe detected rearrangement of the homologous DNA segment in the leukemic cells and in follicular lymphoma cells with the t(14;18) chromosome translocation but not in other neoplastic or normal B or T cells. The probe appears to identify bcl-2, a gene locus on chromosome 18 (band q21) that is unrelated to known oncogenes and may be important in the pathogenesis of B-cell neoplasms with this translocation.

225. MOLECULAR CLONING OF THE CHROMOSOMAL BREAKPOINT OF B-CELL LYMPHOMAS AND LEUKEMIAS WITH THE T(11;14) CHROMOSOME TRANSLOCATION

Tsujimoto Y, Yunis J, Onorato-Shoue L, Erikson J, Nowell PC, Croce CM
Graduate Group of Molecular Biology, University of Pennsylvania, Philadelphia.
Science; 226(4656):1403-6 1984

The chromosomal breakpoint of chronic lymphocytic leukemia (CLL) cells of the B-cell type carrying the translocated long arms of chromosomes 11 and 14 [t(11;14) (q13;q32)] was cloned. The breakpoint was found to be within the joining segment of the human heavy chain locus on the translocated long arm of chromosome 14. A probe that is specific for chromosome 11 and that maps immediately 5' to the breakpoint on the 14q+ chromosome was isolated. The probe detected a rearrangement of the homologous genomic DNA segment in the parental CLL cells and also in DNA from a diffuse large cell lymphoma with the t(11;14) translocation. This rearranged DNA segment was not present in Burkitt lymphoma cells with the t(8;14) translocation or in nonneoplastic human lymphoblastoid cells. The probe can thus be used to identify and characterize a gene located on band q13 of chromosome 11 that appears to be involved in the malignant transformation of human B cells carrying the t(11;14)

translocation. This gene, named *bcl-1*, appears to be unrelated to any of the known retrovirus oncogenes described to date.

226. LOCALIZATION OF THE ONCOGENE C-ERBA1 IMMEDIATELY PROXIMAL TO THE ACUTE PROMYELOCYTIC LEUKAEMIA BREAKPOINT ON CHROMOSOME 17

Sherr D, Sheppard DM, le Beau M, Rowley JD, San Roman C, Solomon E

Imperial Cancer Research Fund, Lincoln's Inn Fields, London. Ann Hum Genet; 49 (Pt 3):167-71 1985

Using *in situ* hybridization, *c-erbA1* has been mapped immediately distal to the translocation breakpoint on chromosome 17 in fibroblasts with a karyotype 46,XX, t(15;17)(q22;q11). Previous work has shown that *c-erbA1* is proximal to the translocation breakpoint on chromosome 17 in the t(15;17)(q22;q12-21) in acute promyelocytic leukaemia. The oncogene can therefore be localized to the region of chromosome 17 between the breakpoints in 17q11 and 17q12-21.

227. GERM-LINE CHROMOSOMAL LOCALIZATION OF HUMAN C-ERB-A ONCOGENE

Jhanwar SC, Chaganti RS, Croce CM

Laboratory of Cancer Genetics and Cytogenetics, Memorial Sloan-Kettering Cancer Center, New York, New York. Somatic Cell Mol Genet; 11(1):99-102 1985

The human germ-line position of *c-erbA*, the cellular counterpart of *v-erbA*, has been determined by *in situ* molecular hybridization of a 3H-labeled *c-onc* gene probe to meiotic pachytene chromosomes. Both *v-erbA* and *v-erbB* are the *v-onc* genes that are associated with induction of sarcoma and erythroblastosis in chicken by the avian erythroblastosis virus, a rapidly transforming RNA tumor virus. The position of *c-erbA*, determined here to be at 17q21.33-q22, is in the same region of chromosome 17 in which a nonrandom break occurs in the generation of t(15;17), a translocation commonly seen in acute promyelocytic leukemia.

228. A HUMAN C-ERBA ONCOGENE HOMOLOGUE IS CLOSELY PROXIMAL TO THE CHROMOSOME 17 BREAKPOINT IN ACUTE PROMYELOCYTIC LEUKEMIA

Dayton AI, Selden JR, Laws G, Dorney DJ, Finan J, Tripputi P, Emanuel BS, Rovera G, Nowell PC, Croce CM

Wistar Institute of Anatomy and Biology, Philadelphia, PA. Proc Natl Acad Sci USA; 81(14):4495-9 1984

A human cDNA library was screened for sequences homologous to the *erbA* gene of avian erythroblastosis virus (AEV). One such clone, *cHerbA-1*, was used to map the chromosomal location of highly homologous human sequences that were found to be present on chromosome 17 as judged by Southern blot screening of a panel of mouse-human hybrid cell lines segregating human chromosomes. *cHerbA-1* was hybridized *in situ* to metaphase chromosomes from a normal male subject and from a female patient with an acute promyelocytic leukemia (APL) having the typical t(15;17) translocation. The results localized the cellular *c-erbA* sequences on chromosome 17 to the q21-q24 region of normal chromosomes and indicated that the *c-erbA* sequences remained on the 17q chromosome in the APL cells, suggesting that they could be assigned to the 17(q21-q22) region. For additional data, we hybridized human neoplastic cells derived from a poorly differentiated acute leukemia carrying a t(17;21) translocation with thymidine kinase (TK)-deficient LMTK- mouse cells. A resulting hybrid, containing only the 21q+ chromosome, did not have human *c-erbA* sequences. Since the breakpoint on 17q in this translocation was similar to that in the APL t(15;17) translocation, this supported the assignment

of *c-erbA* to the q21-q22 region of chromosome 17. The apparent close proximity of the *c-erbA* sequences to the chromosomal breakpoints in these two leukemias suggests a possible role for this oncogene homologue in the development of these neoplasms.

229. A T(1;19) CHROMOSOME TRANSLOCATION IN THREE CASES OF HUMAN MALIGNANT MELANOMA

Parmier AH, Balaban G, Herlyn M, Clark WH Jr, Nowell PC

Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia 19104. Cancer Res; 46(3):1526-9 1986

Abnormalities of chromosome 1, including trisomy for all or a portion of the long arm, have been frequently reported in many cancers. Anomalies of chromosome 19 are far less common, although a t(1;19)(q23;p13) translocation has been reported in association with pre-B-cell leukemia. We have observed a t(1;19)(q12;p13) translocation in three cases of advanced melanoma, with the translocation chromosome representing an extra dose of 1q in each instance. The breakpoint on 1q was within the centromeric heterochromatin, proximal to the site in pre-B-cell leukemia, but the breakpoint on 19p appeared identical. The gene for human insulin receptor has recently been mapped to this region of chromosome 19 (p13.2-13.3). This gene shares structural and sequence homologies with the epidermal growth factor receptor (*erbB* oncogene) and members of the *src* family of oncogenes, suggesting that alterations in the insulin receptor, resulting from chromosomal translocation, could lead to a role in tumorigenesis. The present findings may permit this possibility to be examined in a neoplasm of neuroectodermal origin.

230. GENE FOR HUMAN INSULIN RECEPTOR: LOCALIZATION TO SITE ON CHROMOSOME 19 INVOLVED IN PRE-B-CELL LEUKEMIA

Yang-Feng TL, Francke U, Ullrich A

Department of Human Genetics, Yale University School of Medicine, New Haven, Connecticut 06510. Science; 228(4700):728-31 1985

Consistent chromosomal translocations in neoplastic cells may alter the expression of proto-oncogenes that are located near the breakpoints. The complementary DNA sequence of the human insulin receptor is similar to those of the *BGF* receptor (*erbB* oncogene) and products of the *src* family of oncogenes. With *in situ* hybridization and Southern blot analysis of somatic cell hybrid DNA, the human insulin receptor gene was mapped to the distal short arm of chromosome 19 (bands p13.2 - p13.3), a site involved in a nonrandom translocation in pre-B-cell acute leukemia.

231. A HUMAN C-SRC GENE RESIDES ON THE PROXIMAL LONG ARM OF CHROMOSOME 20 (CEN - Q131)

Sakaguchi AY, Meléndez T, Naylor SL

Department of Medicine, University of Texas Health Science Center, San Antonio 78204. Cancer Genes Cytogenet; 18(2):123-9 1985

A molecular clone of *v-src*, the oncogene of Rous sarcoma virus, was used to detect and regionally localize a human *c-src* proto-oncogene on chromosome 20. The human *c-src* gene, detected as either a 28-kbp *EcoRI* DNA fragment or as a 15.4-kbp *BglII* DNA fragment, was localized to 20cen - q131 by filter hybridization analysis of DNAs from human-rodent somatic cell hybrids. The results indicate that *c-src* is on the same chromosome arm as aberrations associated with myeloproliferative disease, although the possible involvement of *c-src* in these aberrations is unknown.

232. REGIONAL MAPPING OF THE HUMAN PROTO-ONCOGENE C-YES-1 TO CHROMOSOME 18 AT BAND Q21.3

Yoshida MC, Suzuki M, Mizu K, Semba K, Nishizawa M, Yamamoto T, Toyoshima K
Chromosome Research Unit, Faculty of Science, Hokkaido University, Sapporo.
Jpn J Cancer Res; 76(7):559-62 1985

Human proto-oncogene c-yes-1 homologous to the viral oncogene (v-yes) of an avian Y73 sarcoma virus was mapped to region q21.3 of chromosome 18 by in situ hybridization. This finding confirmed and more rigidly substantiated the previous assignment which was based on analyses of human X mouse somatic cell hybrids and Southern blots.

233. ACTIVATION OF A NOVEL HUMAN TRANSFORMING GENE, RET, BY DNA REARRANGEMENT

Takahashi M, Ritz J, Cooper GM
Laboratory of Molecular Carcinogenesis, Dana-Farber Cancer Institute, Boston, Massachusetts 02115.
Cell; 42(2):581-8 1985

A novel transforming gene was detected by transfection of NIH 3T3 cells with human lymphoma DNA. The tumor DNA induced a single focus in primary transfections, whereas DNAs of transformed NIH cells induced transformation with high efficiencies in secondary and tertiary assays. Molecular clones spanning about 37 kb of human sequence were isolated from tertiary transformant DNA. Blot hybridization indicated that the transforming gene consisted of two segments that were unlinked in both normal human and primary lymphoma DNAs. The two segments of human DNA were cotranscribed in transformed NIH cells but not in any human cells examined. The transforming gene thus appeared to be activated by recombination between two unlinked human DNA segments, possibly by cointegration during transfection.

234. EXPRESSION OF THE HUMAN C-FMS PROTO-ONCOGENE IN HEMATOPOIETIC CELLS AND ITS DELETION IN THE 5q- SYNDROME

Nienhuis AW, Bunn HF, Turner PH, Gopal TV, Nash WG, O'Brien SJ, Sberri CJ
Clinical Hematology Branch, National Heart, Lung and Blood Institute, Bethesda, Maryland 20205.
Cell; 42(2):421-8 1985

The c-fms proto-oncogene was shown to be expressed in human bone marrow and in differentiated blood mononuclear cells, suggesting that its gene product plays a role in hematopoietic maturation. The c-fms mRNA was not detected in HL-60 cells, an established promyelocytic line, whereas c-fms expression appeared 48 hr after induction when most cells had differentiated into macrophages. An acquired deletion of chromosome 5 (5q-) in bone marrow cells is associated with abnormalities in blood cell production. The normal 5 and 5q- chromosomes were segregated by construction of cell hybrids between bone marrow and rodent cells. A selective system was used that requires retention of the structural gene for dihydrofolate reductase, located on human chromosome 5. Analysis of DNA from individual hybrid clones revealed that the 5q- deletion had removed the c-fms gene. We postulate that hemizygosity at the c-fms locus leads to abnormalities in hematopoietic maturation.

235. LOCALIZATION OF GENE FOR HUMAN P53 TUMOUR ANTIGEN TO BAND 17P13

Isobe M, Emanuel BS, Givol D, Oren M, Croce CM
Wistar Institute, Philadelphia, Pennsylvania.
Nature; 320(6057):84-5 1986

Recently the gene for the cellular tumour antigen p53, a phosphoprotein found in increased concentration in a variety of human cells, had been mapped to region 17q22 by in situ hybridization techniques and has been shown to translocate to the chromosome carrying the translocation [t(15; 17)] associated with acute promyelocytic leukaemia (APL). Based on this finding it has been postulated that this gene has a role in the pathogenesis of APL. Here we present evidence that the gene for p53 is not located on the long arm of chromosome 17, but maps to band 17p13. We therefore suggest that this gene is not directly involved in the chromosome translocation observed in APL.

236. THE GENE FOR HUMAN P53 CELLULAR TUMOR ANTIGEN IS LOCATED ON CHROMOSOME 17 SHORT ARM (17P13)

McBride OW, Merry D, Givol D
Laboratory of Biochemistry, National Cancer Institute, Bethesda, MD 20892.
Proc Natl Acad Sci USA; 83(1):130-4 1986

A clone that cross-hybridizes with a mouse p53 probe has been isolated from a cDNA library of simian virus 40-transformed human fibroblasts. This cloned human p53 cDNA was used as a probe to examine DNAs obtained from human-rodent somatic cell hybrids that have segregated human chromosomes. The results show that the human p53 gene is located on chromosome 17. In addition, Southern analysis of hybrids prepared from human cells containing a chromosome 17 translocation allowed regional localization of the human p53 gene to the most distal band on the short arm of this chromosome (17p13). Localization of the p53 gene to 17p13 was confirmed by in situ hybridization of metaphase spreads with the human p53 probe.

237. HUMAN P53 GENE LOCALIZED TO SHORT ARM OF CHROMOSOME 17

Miller C, Mohandas T, Wolf D, Prokocimer M, Roter V, Koeffler HP
Department of Medicine, UCLA Medical Center 90024.
Nature; 319(6056):783-4 1986

The p53 gene codes for a nuclear protein that has an important role in normal cellular replication. The concentration of p53 protein is frequently elevated in transformed cells. Transfection studies show that the p53 gene, in collaboration with the activated ras oncogene, can transform cells. Chromosomal localization may provide a better understanding of the relationship of p53 to other human cellular genes and of its possible role in malignancies associated with specific chromosomal rearrangements. A recent study mapped the human p53 gene to the long arm of chromosome 17 (17q21-q22) using in situ chromosomal hybridization. Here, by Southern filter hybridization of DNAs from human-rodent hybrids, we have localized the p53 gene to the short arm of human chromosome 17.

238. TRANSLOCATION OF THE P53 GENE IN T(15;17) IN ACUTE PROMYELOCYTIC LEUKAEMIA

Le Beau MM, Westbrook CA, Diaz MO, Rowley JD, Oren M
Department of Medicine, University of Chicago, Illinois 60637.
Nature; 316(6031):826-8 1985

Recent studies have demonstrated that the cellular tumour antigen p53 (ref. 1) can complement activated ras genes in the transformation of rat fibroblasts, suggesting that the gene

encoding p53 may act as an oncogene. Here, by using in situ chromosomal hybridization, we have mapped the p53 gene to human chromosome 17, at bands 17q21-q22, the region containing one of the breakpoints in the translocation t(15;17) (q22;q21) associated with acute promyelocytic leukaemia (APL). Hybridization of p53 and erb-A (17q11-q12) probes to malignant cells from three APL patients indicated that the p53 gene is translocated to chromosome 15 (15q+), whereas erb-A remains on chromosome 17. Analysis of variant translocations demonstrates that the 15q+ chromosome contains the conserved junction, suggesting a role for p53 in the pathogenesis of APL. However, rearrangements of the p53 gene were not detected on Southern blotting of DNA from leukaemic cells of four APL patients with t(15;17).

239. EVIDENCE FOR TWO DISTINCT C-SRC LOCI ON HUMAN CHROMOSOMES 1 AND 20

Le Beau MM, Westbrook CA, Diaz MO, Rowley JD
Department of Medicine, University of Chicago, Illinois.
Nature; 312(5989):70-1 1984

A number of proto-oncogenes have recently been localized to the chromosomal segments that are the breakpoints in the specific rearrangements noted in human malignant diseases. Moreover, rearranged forms of several proto-oncogenes have been identified in malignant cells; in several instances, the proto-oncogene has undergone an alteration as a result of a nonrandom chromosomal rearrangement. One proto-oncogene that has yet to be associated with human neoplastic disease is c-src, the cellular homolog of the transforming sequence of Rous sarcoma virus (RSV). By somatic cell hybridization, c-src has been mapped to chromosome 20, but its precise location was not determined. We have now mapped this gene by using in situ hybridization of the cloned human c-src probe to human mitotic chromosomes. We report here that the human genome contains two loci with strong homology to the coding regions of this oncogene, at 1p34-p36 and 20q12-q13. It is noteworthy that these chromosomal regions are frequently involved in the structural rearrangements observed in haematological malignant diseases.

240. GENETIC ANALYSIS OF THE 15;17 CHROMOSOME TRANSLOCATION ASSOCIATED WITH ACUTE PROMYELOCYTIC LEUKEMIA

Speer D, Hiorns LR, Stanley KF, Goodfellow PN, Swallow DM, Povey S, Heisterkamp N, Groffen J, Stephenson JR, Solomon E
Imperial Cancer Research Fund, Lincoln's Inn Fields, London, United Kingdom.
Proc Natl Acad Sci USA; 80(16):5007-11 1983

Somatic cell hybrids have been constructed between a thymidine kinase-deficient mouse cell line and blood leukocytes from a patient with acute promyelocytic leukemia showing the 15q+;17q- chromosome translocation frequently associated with this disease. One hybrid contains the 15q+ translocation chromosome and very little other human material. We have shown that the c-fes oncogene, which has been mapped to chromosome 15, is not present in this hybrid and, therefore, probably is translocated to the 17q- chromosome. Analysis of the genetic markers present in this hybrid has enabled a more precise localization of the translocation breakpoints on chromosomes 15 and 17. Our experiments also have enabled an ordering and more precise mapping of several genetic markers on chromosomes 15 and 17.

241. CHROMOSOMAL LOCALIZATION OF HUMAN CELLULAR HOMOLOGUES OF TWO VIRAL ONCOGENES

Heisterkamp N, Groffen J, Stephenson JR, Spurr NK, Goodfellow PN, Solomon E, Carris B, Bodmer WF
Lab. Viral Carcinogenesis, NCI, FCRF, Frederick, MD, 21701
Nature; 299(5885):747-749 1982

Acute transforming RNA tumor viruses represent genetic recombinants between type C retroviral sequences and transformation-specific sequences of cellular origin. Of the known mammalian cell-derived transforming genes (oncogenes), two have been shown to encode proteins with either intrinsic or highly associated tyrosine-specific protein kinase activity. One such gene, c-fes, is of cat cellular origin, while the second, c-abl, was derived from mouse cellular sequences. We now show that the human equivalents of c-fes and c-abl are localized on human chromosomes 15 and 9, respectively. These findings exclude the possibility that these transformation-related genes are clustered at a single locus within the human genome. It is of interest that both of these chromosomes are involved in specific rearrangements found in certain forms of human cancer. (Author abstract) (41 Refs)

D.

REVIEWS AND GENERAL STUDIES OF ONCOGENES ASSOCIATED WITH TRANSLOCATIONS

242. CHROMOSOMAL ABNORMALITIES IN LEUKEMIA AND LYMPHOMA: CLINICAL AND BIOLOGICAL SIGNIFICANCE (104 Refs)

Le Beau MM, Rowley JD
Department of Medicine, University of Chicago, Illinois 60637.
Adv Hum Genet; 15:1-54 1986

Keywords (MeSH): Acute Disease; Burkitt's Lymphoma/familial and genetic; *Chromosome Aberrations; Chromosome Deletion; Genetic Marker; Human; Karyotyping; Leukemia/chemically induced/classification/*familial and genetic; Leukemia, Lymphoblastic/familial and genetic; Leukemia, Monoblastic/familial and genetic; Leukemia, Myeloblastic/familial and genetic; Leukemia, Myelocytic/familial and genetic/pathology; Lymphoma/classification/*familial and genetic; Oncogenes; Philadelphia Chromosome; Ploidies; Prognosis; Review; Translocation (Genetics).

243. CHRONIC LEUKEMIAS: ONCOGENES, CHROMOSOMES, AND ADVANCES IN THERAPY [CLINICAL CONFERENCE] (191 Refs)

Champlin R, Gale RP, Foon KA, Golde DW
Department of Medicine, UCLA School of Medicine.
Ann Intern Med; 104(5):671-88 1986

Keywords (MeSH): Antibodies, Monoclonal/therapeutic use; Bone Marrow/transplantation; *Chromosome Aberrations; Chronic Disease; Human T-Cell Leukemia Virus; Human; Interferon Type I/therapeutic use; *Leukemia/etiology/familial and genetic/therapy; Leukemia, Hairy Cell/complications/therapy; Leukemia, Myelocytic/familial and genetic/therapy; Lymphoproliferative Disorders/therapy; *Oncogenes; Postoperative Complications; Recombinant Proteins/therapeutic use; Retrovirus Infections; Review; Splenectomy; Transcription, Genetic; Translocation (Genetics).

244. [CHROMOSOME TRANSLOCATIONS AND CELLULAR ONCOGENES IN HEMATOLOGIC NEOPLASMS]

Sakurai M

Dept. of Cancer Chemotherapy Saitama Cancer Center Hospital,
Gan To Kagaku Ryobo; 13(3 Pt 2):652-60 1986

Chromosome translocations found in hematologic malignant diseases are correlated with the cytologic and histologic features of the neoplastic cells as well as with clinical features, such as the patient's age, response to therapy and prognosis. Thus, the 8; 21 and 15; 17 translocations, respectively, are associated with acute myeloblastic and acute promyelocytic leukemias. Likewise, the 8q24 translocations including 8; 14, 2; 8, and 8; 22 translocations seen in Burkitt's lymphoma, and the 1; 19 and 11; 14 translocations seen associated with pre-B-cell and T-cell leukemias, respectively, are examples of similar correlations with regard to lymphoproliferative disorders. With the exception of the cases of 9; 22 (Ph1) and 11q23 translocations, each of which is found in both myeloid and lymphoid neoplasms, any one abnormality is rarely encountered in association with both categories of malignancy. Recent studies indicate that, with regard to many of the known chromosome translocations, the break occurs at a point close to the location of a specific cellular oncogene. Thus, c-myc and c-abl, which reside in 8q24 and 9q34, respectively, are known to undergo rearrangement in cases of 8q24 and 9; 22 translocations. These rearrangements have been proved to give rise to the production of an abnormal protein, which seems to cause the malignant transformation of cells with such chromosome translocations. Chromosome translocations are now believed to be directly related to oncogenesis through the mechanism of activation of the cellular proto-oncogene.

245. NEOPLASTIC TRANSFORMATION OF THE PLURIPOTENTIAL STEM CELL. I. POSSIBLE MOLECULAR MECHANISMS OF NEOPLASTIC TRANSFORMATION (102 Refs)

Rupniewska ZM

Acta Haematol Pol; 16(1-2):90-101 1985

Keywords (MeSH): Animal; Cell Differentiation; Cell Transformation, Neoplastic/*pathology; Gene Expression Regulation; Hematopoietic Stem Cells/*pathology; Human; Leukemia, Myeloblastic/*etiology; Leukemia, Myelocytic/*etiology; Lymphoma/*etiology; Mice; Models, Genetic; *Oncogenes; Review; Translocation (Genetics).

246. THE MOLECULAR BIOLOGY OF CHROMOSOME ALTERATIONS IN MYELOGENOUS LEUKEMIA

Drabkin HA

West J Med; 143(6):825-8 1985

Keywords (MeSH): Chromosome Mapping; Chromosomes, Human, 13-15; Chromosomes, Human, 21-22; Chromosomes, Human, 6-12; Human; Leukemia/secondary; Leukemia, Myeloblastic/*familial and genetic; Leukemia, Myelocytic/*familial and genetic; Oncogenes; Philadelphia Chromosome; *Translocation (Genetics).

247. CHROMOSOME 1 ABERRATIONS IN CANCER

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Department of Cancer Research, Mount Vernon Hospital,
Northwood, Middlesex, England.
Cancer Genet Cytogenet; 21(4):279-85 1986

Evidence for chromosome involvement in structural rearrangements in cancer is reviewed. There have been adequate studies of cancer at most of the common sites, and at all of these, nonrandom chromosome involvement has been demonstrated. In general, a variety of changes is encountered, irrespective of the site; most commonly, however, the changes result in the duplication of long arm material. It seems that

these nonrandom changes, which tend to occur at a relatively late stage, may contribute to the progression of all forms of cancer. However, a small number of chromosome aberrations are also now known, which may represent specific and possibly initiating changes in particular forms of cancer. These include short arm deletions in neuroblastoma and translocations in leukemias and myelodysplasia. (84 Refs)

248. ANALYSIS OF G Banded KARYOTYPES IN MYELOMA CELLS

Chen KC, Bevan PC, Matthews JG

Department of Haematological Medicine, University Clinical School,
Cambridge.

J Clin Pathol; 39(3):260-6 1986

Karyotypes of bone marrow cells from 24 patients with multiple myeloma (MM) and two patients with de novo plasma cell leukaemia (PCL) were analysed by Giemsa banding (G banding). Chromosome aberrations were found in 13 patients with MM and both patients with PCL. Hyperdiploid and hypodiploid lines were present in eight and five of the patients with MM, respectively. Marker chromosomes derived from structural rearrangements were present in all eight cases of MM with hyperdiploid lines, although markers of uncertain origin were rare in those patients with hypodiploid lines. Chromosome 1 participated most often, and chromosomes 5 and 9 often played a part in the structural rearrangements. Chromosomes 3, 5, 7, 9, 11, 15, 19, and 21 were subject to numerical aberrations. In the two patients with PCL one had a hypodiploid line with a 14q+ marker derived from a t(11;14) and the other a hyperdiploid line. The breakpoints on the chromosomes participating in the structural rearrangements in myeloma showed a good correlation with known fragile sites and oncogene locations on the corresponding chromosomes.

249. HISTORY AND PRESENT STATUS OF HUMAN CHROMOSOME STUDIES

Tjio JH, Nichols WW

National Institutes of Health, Bethesda, Maryland 20205.

In Vitro Cell Dev Biol; 21(6):305-13 1985

Keywords (MeSH): Burkitt's Lymphoma/familial and genetic; Chromosome Abnormalities/familial and genetic; *Chromosomes, Human/ultrastructure; Colchicine/diagnostic use; Cytogenetics; Eye Neoplasms/familial and genetic; Female; Historical Article; History of Medicine, 20th Cent.; Human; Karyotyping; Mutation; Neoplasms/familial and genetic; Retinoblastoma/familial and genetic; Sea Urchins/genetics; Translocation (Genetics); X Chromosome/ultrastructure.

250. SEQUENCE REARRANGEMENTS AND GENOME INSTABILITY. A POSSIBLE STEP IN CARCINOGENESIS

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Poland.

J Cancer Res Clin Oncol; 109(3):159-72 1985

A substantial part of the mammalian genome is composed of sequences that do not contain structural genes. These sequences may constitute the major target for physical, chemical and biological DNA-damaging agents and can be involved in carcinogenesis. DNA-damaging agents contribute to the instability of the genome by introducing recombination-prone sites at DNA; these agents lead to extensive chromosomal lesions and rearrangements of genes and their regulatory sequences. Movable sequences that exist and operate in certain bacteria, yeast, and the fruit fly are responsible for sequence rearrangements and contribute to the majority of mutations. Their presence and role in higher animals is not

well established. Extensive chromosomal rearrangements were identified in numerous malignancies in man and animals and definitely seem to represent a characteristic of malignancy. Vast chromosomal damage and sequence reshuffling may be of no less importance in the malignant transformation than the point mutation of a particular gene. (65 Refs)

251. SIGNIFICANCE OF CHROMOSOME REARRANGEMENTS IN LEUKEMIA AND LYMPHOMA

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Life Sci Res Rep; 30:179-202 1985

Application of new chromosome banding techniques over the past decade has resulted in major advances in understanding of the specificity of chromosome abnormalities associated with human tumors. Chromosome abnormalities that have been identified in human leukemias and in other malignant diseases include the following: gain of a whole chromosome or portion thereof; loss of part or all of a chromosome; consistent translocations; and other structural rearrangements. In chronic myeloid leukemia, a reasonably consistent translocation, $t(9;22)(q34;q11)$, is observed in 93% of Philadelphia(1)-positive patients. In acute nonlymphocytic leukemia, $t(8;21)(q22;q22)$ is found almost exclusively in patients with acute myeloblastic leukemia with maturation, whereas $t(15;17)(q22;q21)$ is seen only in patients with acute promyelocytic leukemia. An inversion of chromosome 16($p13q22$) has been described recently in patients with acute myelomonocytic leukemia and abnormal marrow eosinophils; other patients with marrow eosinophilia had a deletion of 16 at $q22$. Translocations or deletions involving 11 $q23$ have been described in patients with acute monocytic leukemia, particularly of the monoblastic type. Various translocations have been observed in B-cell acute lymphoblastic leukemia or in Burkitt's lymphoma; the most common of these is $t(8;14)(q24;q32)$, but variants have been observed in which the consistent change involved is 8 $q24$. The various immunoglobulin loci are located on chromosomes 2, 14, and 22 in the same chromosome band that is affected by the translocations in B cell leukemia. The *myc* gene has been found at 8 $q24$; translocation results in the movement of the *myc* gene adjacent to the Ig locus on chromosome number 14. These translocations may occur randomly, but if a selective advantage is conferred, then proliferation of the aneuploid line could occur in relation to cells with a normal karyotype. (44 Refs)

252. AN APPRAISAL OF THE APPLICATION OF RECOMBINANT DNA TECHNIQUES TO CHROMOSOME DEFECTS (15 Refs)

Elliott KP, Davies KE

Biochemistry Department, St. Mary's Hospital Medical School, London, U.K.

Biochem J; 226(1):1-11 1985

Keywords (MeSH): Chromosome Abnormalities/*familial and genetic; DNA, Recombinant/*diagnostic use; Female; Gene Expression Regulation; Genotype; Hereditary Diseases/*familial and genetic; Human; Male; Methods; Neoplasms/familial and genetic; Pedigree; Phenylketonuria/familial and genetic; Review; Translocation (Genetics).

253. APPLICATION OF CYTOGENETICS IN NEOPLASTIC DISEASES

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CRC Crit Rev Clin Lab Sci; 22(3):219-74 1985

This review will concern itself with the application of cytogenetic findings in neoplastic diseases. This application can be divided into two general categories: practical and theoretical. The practical applications reside in utilizing karyotypic changes, particularly in leukemias and lymphomas, not only for diagnostic purposes but also for predicting response to therapy and prognosis. This is especially evident in the various acute nonlymphocytic leukemias and in most of the acute lymphoblastic leukemias. Thus, a definite correlation exists between the cytogenetic findings and the various clinical, laboratory, and cytologic parameters of most of the leukemias. Undoubtedly, these leukemias will ultimately be classified and defined more in terms of their cytogenetic aspects than any other. Though the application in lymphoma is not at the same level as that in leukemia, developments in that field certainly indicate a similar utilization of the cytogenetic findings in these diseases. The presence or absence of a Ph1 chromosome in a chronic myelocytic leukemia has been utilized widely, not only in the diagnosis but also in the predictability of response; the cytogenetic findings have also been utilized in predicting the blastic phase of disease. The list of specific chromosome changes in various solid tumors is of a lesser number, but significant developments indicate that the applicability of chromosome changes in these diseases will, also, be established in the near future. The application of chromosome findings to theoretical aspects of malignancy has assumed an important place recently in the demonstration that so-called oncogenes (or proto-oncogenes) are located or associated with areas of human chromosomes in which breaks and translocations are involved. Thus, it appears that chromosome changes in human malignancy, once their specificity is established, are important parameters in the clinical and theoretical aspects of the disease. A discussion will also be given on primary vs. secondary chromosome changes and their significance in the biology and behavior of the malignancy. (155 Refs)

254. ON THE MEANING OF FRAGILE SITES IN CANCER RISK AND DEVELOPMENT

Shabtai F, Klar D, Hart J, Halbrecht I

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Cancer Genet Cytogenet; 18(1):81-5 1985

In the last few years, there has been increasing concern about the possible involvement of fragile sites in cancer risk and development. Patients with malignancies and family histories of cancer who presented with constitutional fragile sites are reported here. These findings are discussed with regard to the familial risk for cancer and the tissue specificity of the malignancy in relation to the different fragile sites. The hypothesis is advanced that these may be sites of viral DNA modification, probably representing areas where genes that are important for the metabolism of the virus are located. On the other hand, these genes may well be cellular (proto)oncogenes. We believe that fragile sites may increase the risk for cancer, not by being break-prone points at oncogene locations, but through more complex mechanisms that are not easy to predict.

255. NEOPLASIA AND CHROMOSOMAL BREAKAGE IN ATAXIA-TELANGEICTASIA: A 2:14 TRANSLOCATION

Davis MM, Gatti RA, Sparkes RS

Department of Medical Microbiology, Stanford University School of Medicine, Palo Alto, California 94305.

KROC Found Ser; 19:197-203 1985

Four common sites of chromosome breakage have been observed in patients with ataxia-telangiectasia (AT): 7p14, 7q35, 14q11.2, and 14q32. These sites appear to coincide with the location of genes for the T-cell receptor subunits (alpha, beta, and gamma) and IGH. Each of these genes involves rearrangements of DNA for its expression, suggesting that an abnormal DNA processing enzyme or family of enzymes underlies this propensity for chromosomal breakage in AT patients. Such a defect could also explain the radiation hypersensitivity of AT fibroblasts. In view of these findings, it is perhaps surprising that AT patients do not manifest more severe immunological defects although they would explain the lack of uniformity of these defects from one patient to the next. Two other genes utilize DNA rearrangement, IGK (on chromosome 2p12) and IGL (on chromosome 22q11), and have not been noted previously to be involved in translocations in these patients. We report here a 2:14 translocation (p14;q32) in a phytohemagglutinin-stimulated lymphocyte from a patient with AT.

256. FRAGILE SITES AND PREDISPOSITION TO LEUKEMIA AND LYMPHOMA

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Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis.

Cancer Genet Cytogenet; 12(1):85-8 1984

Keywords (MeSH): Chromosome Abnormalities/*familial and genetic; Chromosome Banding; Chromosome Mapping; Human; Leukemia/*familial and genetic; Lymphoma/*familial and genetic; Oncogenes; Translocation (Genetics).

257. REPORT OF THE COMMITTEE ON CHROMOSOME REARRANGEMENTS IN NEOPLASIA AND ON FRAGILE SITES (162 Refs)

de la Chapelle A, Berger R

Cytogenet Cell Genet; 37(1-4):274-311 1984

Keywords (MeSH): Bibliography; Chromosome Aberrations; Chromosome Mapping; Chromosomes, Human/*physiology; DNA, Neoplasm/*genetics; Human; Leukemia/familial and genetic; Lymphoma/familial and genetic; Neoplasms/*familial and genetic; Oncogenes; Review.

258. THE ROLE OF GENETIC TRANSPOSITION IN CARCINOGENESIS

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Biochemical Basis of Chemical Carcinogenesis. Griem H, Jung R, Kramer M, Marquardt H, Oesch F, eds. New York, Raven Press, p. 227-32, 1984.

Exposure of an experimental animal to a single dose of a tumor-inducing agent requires a major period of the animal's life span for overt tumor to develop; it is conceivable, therefore, that the initiating event alone is not enough for tumor development. Although the exact nature of the further events that are required is not known, results obtained with experimentally induced tumors and also with human tumors suggest that genetic transposition, visualized either at the chromosome level or at the molecular level, plays a significant role in the genesis of certain tumors. Examples are presented and discussed under the following section headings: chromosome changes (trisomy 15) in murine lymphomas, translocation in murine plasmacytomas, human Burkitt lymphomas and chromosome translocations, promoter insertion

events, and chromosome deletion in human retinoblastoma. The hypothesis is put forward that genetic transposition leads to activation of cellular oncogenes by installing them close to and under the influence of strong cellular promoters. (35 Refs)

259. CHROMOSOMAL REARRANGEMENTS IN BLADDER CANCER (32 Refs)

Gibas Z, Sandberg AA

Department of Genetics and Endocrinology, Roswell Park Memorial Institute, Buffalo, New York.

Urology; 23(3 Suppl):3-9 1984

Keywords (MeSH): Bladder Neoplasms/*familial and genetic; Cell Line; Cells, Cultured; *Chromosome Aberrations; Chromosome Banding; Genetic Marker; Human; Karyotyping; Oncogenes; Prognosis; Review.

260. SOMATIC CELL FUSION AS A SOURCE OF GENETIC REARRANGEMENT LEADING TO METASTATIC VARIANTS

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Department of Biologia e Genetica per le Scienze mediche, University of Milan, Italy.

Cancer Metastasis Rev; 3(3):193-222 1984

Tumor cell populations displaying metastatic properties often have higher gene dosage than their less malignant progenitor tumors, as shown by increased ploidy levels, chromosome duplication and gene amplification. The acquisition by tumor cells of high chromosome numbers may be due to endoreduplication or somatic hybridization either between tumor cells or between tumor and host cells. All such mechanisms increase genetic variability and instability in tumor cells since they trigger a polyploidization-segregation cycle. Among the wide variety of segregants which may emerge from high-ploidy cells, variants with increased malignancy can be positively selected in vivo. Evidence for in vivo fusion of tumor and normal host cells has been reported in different tumor systems. However the attainment by tumor-host hybrids of a higher degree of malignancy has only been observed following substantial chromosome segregation. The involvement of a cell of bone marrow origin as preferential host partner in the fusion process has been proved both by studies on tumor-host hybrids in bone marrow radiation chimeras and in vitro hybridization experiments between non-metastatic tumors and normal lymphoreticular cells which have led to the establishment of metastatic variants. Several different segregational mechanisms may bring about homozygosity or hemizygosity of recessive alleles in tumor-host hybrids, leading to their expression. The marked chromosome dynamics of tumor-host hybrids are also responsible for extensive chromosome rearrangements. At the molecular level these may represent mechanisms causing altered oncogene activity. The activation of new oncogenes by transposition or amplification as well as the amplification of previously activated oncogenes are the mechanisms most likely to be responsible for transition from low to high malignancy, occurring through ploidy changes, such as those produced by somatic mating. (202 Refs)

261. CHROMOSOME ABNORMALITIES IN CANCER DEVELOPMENT

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Environ Sci Res; 31:35-59 1984

Chromosomes in human cancers and prezygotic chromosome mutations in relation to cancer are reviewed. Chromosome abnormalities in human tumors may be classified into (1)

those specific to particular tumors (eg, Philadelphia 1 or 9;22 translocation in chronic myelogenous leukemia) and (2) those common to several types of cancer (eg, polyploidization and loss or gain of such chromosomes at 1q+, i(6p), or i(17q)). Nine cellular oncogenes have recently been assigned to human chromosomes. The mechanisms of site-specific chromosome rearrangements and the involvement of cellular oncogenes, as well as their link to cancer, remain unknown. Some retinoblastoma patients exhibit constitutional chromosome abnormalities involving chromosome 13, as manifested by a partial deletion of its long arm (13q-). An analogous condition has been found in aniridia-Wilms' tumor in the form of an interstitial deletion of chromosome 11p (11p-). Interstitial deletions and reciprocal translocations are associated with human tumors frequently enough to suggest etiological involvement. Generation of tumor-specific and site-specific chromosome mutations appears to be intimately related to the normal functioning of the gene(s) in its particular tissue, such as during growth and development. Prezygotic chromosome lesions often involve deletions or translocations at particular sites of chromosomes, suggesting that deletion, repression, or disruption of the normal expression of particular gene(s) may be a critical event in carcinogenesis. In contrast, the types of chromosome mutations common to a wide variety of tumors include genome reorganization (eg, gene amplification) or elimination of a part of the genome. The high frequency of their occurrence suggests that these abnormalities are primarily related to the progression or propagation of tumor cells, rather than tumor etiology. (107 Refs)

262. RESTRICTED NUMBER OF CHROMOSOMAL REGIONS IMPLICATED IN AETIOLOGY OF HUMAN CANCER AND LEUKAEMIA

Mitelman F

Department of Clinical Genetics, University Hospital, Lund, Sweden.

Nature; 310(5975):325-7 1984

It has been known since the days of Boveri that neoplasia is associated with chromosomal aberration. The introduction, some 10 years ago, of chromosome banding techniques provided the impetus for the description of an immense number of such aberrations, and for the localization to individual chromosome bands of the breaks underlying the aberrations. Hypothetically, the breaks should comprise two essentially different kinds: primary breaks that are actively involved in the malignant development, and secondary breaks, coincidental to this process. In the search for a possible method to identify primary breaks in human cancer, I selected from the catalogue of chromosome aberrations now available those cases that had one single structural aberration as their sole deviation from normality. I report here that the breakpoints thus specified affect a surprisingly limited number of chromosomal regions, and conclude that these regions contain genes of prime importance to cancer development.

263. CHROMOSOMAL ALTERATIONS ASSOCIATED WITH NEOPLASIA

Sandberg AA

Roswell Park Memorial Institute, Buffalo, NY.

Transplant Proc; 16(2):366-9 1984

Keywords (MeSH): *Cell Transformation, Neoplastic; *Chromosome Aberrations; Human; Leukemia/*familial and genetic; Lymphoma/familial and genetic; Neoplasms/*familial and genetic; Translocation (Genetics).

264. THE CHROMOSOMAL BASIS OF HUMAN NEOPLASIA

Yunis JJ

Department of Laboratory Medicine and Pathology, University of Minnesota, Medical School, Minneapolis.

Science; 221(4607):227-36 1983

High-resolution banding techniques for the study of human chromosomes have revealed that the malignant cells of most tumors analyzed have characteristic chromosomal defects. Translocations of the same chromosome segments with precise breakpoints occur in many leukemias and lymphomas, and a specific chromosome band is deleted in several carcinomas. Trisomy, or the occurrence of a particular chromosome in triplicate, is the only abnormality observed in a few neoplasias. It is proposed that chromosomal rearrangements play a central role in human neoplasia and may exert their effects through related genomic mechanisms. Thus, a translocation could serve to place an oncogene next to an activating DNA sequence, a deletion to eliminate an oncogene repressor, and trisomy to carry extra gene dosage.

265. CHROMOSOMES, GENES, AND CANCER: A CLASSIFICATION OF CHROMOSOME ABNORMALITIES IN CANCER

Gilbert F

Division of Medical Genetics, Mount Sinai School of Medicine, New York, N.Y.

JNCI; 71(6):1107-14 1983

Keywords (MeSH): Cell Transformation, Neoplastic/ultrastructure; Chromosome Abnormalities/classification/*familial and genetic; Chromosome Deletion; *Genes; Human; Neoplasms/classification/etiology/*familial and genetic; Oncogenes; Translocation (Genetics).

266. CONSISTENT CHROMOSOME ABNORMALITIES IN HUMAN LEUKEMIA AND LYMPHOMA (93 Refs)

Rowley JD

University of Chicago, Department of Medicine, Franklin McLean Memorial Research Institute, Illinois.

Cancer Invest; 1(3):267-80 1983

Keywords (MeSH): Chromosome Abnormalities/*familial and genetic; Chromosomes, Human, 13-15; Chromosomes, Human, 16-18; Chromosomes, Human, 21-22; Chromosomes, Human, 6-12; Human; Leukemia/*familial and genetic; Lymphoma/*familial and genetic; Review; Translocation (Genetics).

II.

AMPLIFICATION OF ONCOGENES

A.

AMPLIFICATION OF MYC ONCOGENES

1.

Amplification of the C-myc Oncogene

267. COMPARISON OF AMPLIFIED AND UNAMPLIFIED C-MYC GENE STRUCTURE AND EXPRESSION IN HUMAN SMALL CELL LUNG CARCINOMA CELL LINES

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Cancer Res; 46(4 Pt 2):2050-5 1986

A human small cell lung cancer cell line (H82) demonstrates 40- to 50-fold amplification of the c-myc gene but expresses at least 250-fold more steady-state c-myc messenger RNA

than an unamplified small cell lung cancer cell line (H378) with no detectable expression of c-myc. We compared the chromatin structure of c-myc in H82 to that in H378 using DNase I sensitivity and DNA methylation patterns. DNase I hypersensitivity sites were identical in H82 and H378 and were similar to the pattern seen in a B-lymphoblastoid cell line, despite extensive amplification of c-myc in H82. Methylation patterns were also very similar in H82 and H378, with hypomethylation or partial methylation at the c-myc coding regions and the flanking 5' sequences, despite the absence of detectable c-myc expression in H378. Therefore, the predominant chromatin structural patterns do not appear to correlate with observed differences in gene expression. In addition, these studies demonstrate that the patterns of DNase I hypersensitivity and of methylation can remain intact during a 40-50-fold gene amplification, as observed for the c-myc gene in H82.

268. EVIDENCE FOR REARRANGEMENT, AMPLIFICATION, AND EXPRESSION OF C-MYC IN A HUMAN GLIOBLASTOMA

Trent J, Melzer P, Rosenblum M, Harsh G, Kinzler K, Mathal R, Feinberg A, Vogelstein B

Department of Radiation Oncology, University of Arizona, Tucson 85724

Proc Natl Acad Sci USA; 83(2):470-3 1986

Amplified cellular genes are frequently manifested in one of two cytologically recognizable forms, double minutes or homogeneously staining regions. Additionally, evidence is accumulating that aberrant expression of cellular genes (including oncogenes) may be mediated by gene amplification. We now describe the amplification and expression of the cellular oncogene c-myc in double-minute-containing cells from a patient with glioblastoma multiforme, and we have shown that the amplification is associated with rearrangement of the c-myc gene. This finding further supports the common association of the myc gene family in neurogenic tumors and provides evidence of myc gene amplification in human brain cancer.

269. ALTERATIONS OF MYC, MYB, AND RASHA PROTO-ONCOGENES IN CANCERS ARE FREQUENT AND SHOW CLINICAL CORRELATION

Yokota J, Tsunetsugu-Yokota Y, Battifora H, Le Fevre C, Cline MJ

Department of Medicine, Center for Health Sciences, University of California at Los Angeles 90024

Science; 231(4735):261-5 1986

Alterations of c-myc, c-rasHa, or c-myb oncogenes were found in more than one-third of human solid tumors. Amplification of c-myc occurred in advanced, widespread tumors or in aggressive primary tumors. Apparent allelic deletions of c-rasHa and c-myb can be correlated with progression and metastasis of carcinomas and sarcomas.

270. REGULATION OF C-MYC EXPRESSION DURING GROWTH AND DIFFERENTIATION OF NORMAL AND LEUKEMIC HUMAN MYELOID PROGENITOR CELLS

Gowda SD, Kaler RD, Bagby GC Jr

Department of Medical Genetics, Oregon Health Sciences University, Portland

J Clin Invest; 77(1):271-8 1986

C-myc proto-oncogene transcripts from serially harvested, colony-stimulating activity (CSA)-stimulated, normal progenitor-enriched human bone marrow cells were compared to those of the promyelocytic leukemia cell line HL-60 and to those of freshly obtained human myeloid leukemic cells. During the early culture period both normal and leukemic cells expressed the c-myc oncogene. In normal cells maximal

expression occurred after 24 h of culture and did not occur in the absence of CSA. At this time, progenulocytes predominated in the cultured cells. Although cellular proliferation occurred for 96 h in vitro, c-myc expression ceased after 24-36 h. Terminally differentiated cells predominated in these cultures by 120 h. In contrast, although leukemic cells also expressed c-myc in vitro, transcription persisted throughout the culture period and, in the case of HL-60 cells, occurred in the absence of exogenous CSA. We also noted that normal cells with only one diploid gene copy exhibited, after 24 h of culture, only twofold fewer transcripts than did HL-60 cells in which there were 16 myc copies. Furthermore, c-myc mRNA degradation rates were similar in normal cells and in HL-60 cells. We conclude that c-myc transcription is a normal event in granulopoiesis linked to proliferative activity as well as to primitive developmental stage. Furthermore, the most consistent abnormality in leukemic cells in vitro is their failure to suppress transcriptional activity of this gene. We suggest that c-myc transcription in HL-60 cells may be appropriate for cells arrested at that developmental stage and that the amplified genes in HL-60 cells are quiescent relative to c-myc in normal cells at the same differentiation stage. The techniques described herein may be of value in identifying mechanisms by which normal hematopoietic cells suppress c-myc expression and aberrancies of these mechanisms in leukemic cells.

271. VARIATION IN MYC GENE AMPLIFICATION AND EXPRESSION IN SUBLINES OF HL60 CELLS

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Beatson Institute for Cancer Research, Gartnavel Estate, Bearsden, Glasgow, Scotland

Leuk Res; 9(2):239-47 1985

Three sublines of the human promyelocytic leukaemia cell line HL60 have been isolated. Histochemical, karyotypic and immunological analyses have confirmed the identity of the three sublines as HL60. However, the extent to which c-myc homologous DNA sequences are amplified in the genomes of these cells varies from 4- to 30-fold. Moreover, the relative abundance of c-myc-related RNA sequences in uninduced cells of each subline is directly proportional to the gene copy number. It is concluded that, while high levels of the c-myc gene and its transcripts may have had a role in the establishment of HL60 cells, these are not required for maintenance of the HL60 phenotype. However we cannot rule out the possibility that a low level of amplification and enhancement of transcription has a role in maintenance of this phenotype.

272. ANALYSIS OF THE EXPRESSION OF THE ONCOGENE C-MYC IN HUMAN BREAST ADENOCARCINOMA

Guerin M, Lacombe MJ, Riou G

Laboratoire de Pharmacologie clinique et moléculaire; Institut

Gustave-Roussy, Villejuif

C R Acad Sci (III); 301(20):833-8 1985

The c-myc oncogene was characterized and its expression analyzed in 32 mammary adenocarcinomas and in 2 benign breast tumors from 34 untreated patients. Southern blot hybridization experiments have demonstrated the amplification of the oncogene (3 to 30 fold) in 3 carcinomas. The analysis of total RNA by Northern blot revealed the presence of a 2.4 kb c-myc RNA band. In 7 out of 10 carcinomas from patients with 3 or more than 3 lymph node metastases the level of c-myc expression evaluated by dot blot analysis was 4 to 14 fold greater than that of normal human tissues. In only 5 out of 22 carcinomas from patients without lymph node metastases or less than 3 invaded nodes the level of c-myc ex-

pression was also higher (4 to 10 fold). The level of c-myc expression was not significantly enhanced in the 2 benign tumors. It is suggested that the c-myc gene activation could be associated to a higher degree of malignancy of mammary carcinomas.

273. AMPLIFICATION OF THE EXPRESSION OF THE C-MYC ONCOGENE IN BRONCHIAL EPIDERMOID CARCINOMA IN MAN

Douc-Rasy S, Terrier P, Krenny JL, Amouroux J, Riou G
Laboratoire de Pharmacologie clinique et moléculaire, Institut
Gustave-Roussy, Villejuif.
C R Acad Sci I/II; 301(13):621-6 1985

Squamous cell lung carcinomas from 10 untreated patients were examined for the state of the oncogene c-myc. Blot hybridization experiments have demonstrated the amplification of the oncogene of about six fold in only one tumor. The oncogene amplification was not detected in normal tissues of patients. The analysis of RNA by Northern blot revealed the presence in the seven tumors examined of a 2.4 kb c-myc RNA band. The level of c-myc expression evaluated by dot blot analysis was 5 to 14 fold greater in tumors than that of histologically normal lung of the same patients.

274. EFFECT OF NEPLANOCIN A ON DIFFERENTIATION, NUCLEIC ACID METHYLATION, AND C-MYC MRNA EXPRESSION IN HUMAN PROMYELOCYTIC LEUKEMIA CELLS

Lisovsky J, Cohen MB, Hartman KD, Knobe MC, Glazer RI
Laboratory of Biological Chemistry, National Cancer Institute,
Bethesda, Maryland 20205.
Mol Pharmacol; 28(1):45-50 1985

The effect of the cyclopentenyl adenosine analog neplanocin A (NPC) on cell growth and differentiation was examined in the human promyelocytic leukemia cell line HL-60. Continuous exposure of HL-60 cells to 0.1-3.3 microM NPC resulted in a progressive reduction in cell growth which was accompanied by an increase in differentiation to cells with a myelocyte and neutrophil morphology. The latter effect was expressed as an increase in the capacity of cells to reduce nitro blue tetrazolium and reached a level of 40% of the total cell population. Preceding the phenotypic changes was the preferential inhibition of RNA and DNA methylation in comparison to inhibition of their synthesis which coincided with the formation of a metabolite of NPC with the chromatographic characteristics of S-adenosyl-L-methionine (AdoMet). In addition, c-myc mRNA expression, which is amplified in HL-60 cells, was markedly reduced following NPC treatment. These results indicate that NPC is an effective inhibitor of RNA and DNA methylation resulting from its conversion to an analog of AdoMet, and that these effects appear to be responsible for reduced c-myc RNA expression and the induction of myeloid differentiation in this cell line.

275. CHROMATIN STRUCTURE OF THE C-MYC GENE IN HL-60 CELLS DURING ALTERATIONS OF TRANSCRIPTIONAL ACTIVITY

Grosso LE, Pitot HC
Department of Oncology, McArdle Laboratory for Cancer Research,
University of Wisconsin-Madison 53706.
Cancer Res; 45(10):5035-41 1985

HL-60 cells have an elevated level of cellular myc RNA due to an amplified c-myc gene. Subsequent to chemically induced differentiation of HL-60 cells, both cellular myc RNA levels (Grosso, L. E., and Pitot, H. C., Biochem. Biophys. Res. Commun., 119: 473, 1984) and myc-specific transcription decrease (Grosso, L. E., and Pitot, H. C., Cancer Res., 45: 847-850, 1985). We have compared the primary DNA structure, DNA methylation, and S1 nuclease sensitivity of the

myc protooncogene in HL-60 cells before and after chemically induced differentiation. We find no change in the structure or methylation of the c-myc gene. The protooncogene is hypomethylated at CCGG sequences in the 5' region but is extensively methylated at sites detected by sequences homologous to the 3' exon or 3' flanking sequences. Four S1 nuclease-sensitive sites are detected prior to differentiation. After the induction of either myeloid or monocytic differentiation, three of the S1 nuclease-sensitive sites are present. The presence of the fourth S1 nuclease-sensitive site correlates with the transcriptional activity of this gene.

276. BIOLOGY OF SMALL CELL LUNG CANCER

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Ireland
Clin Oncol; 4(1):31-43 1985

The in vitro cloning of small cell lung cancer (SCLC) specimens, and the establishment and characterization of continuous SCLC cell lines are reviewed. Experimental techniques are described. In spite of the ability to successfully clone SCLC cells from the majority of tumor positive specimens, there is a paucity of data correlating in vitro responses to chemosensitivity with observed clinical responses. Two major problems exist in the application of the clonogenic assay of SCLC specimens: (1) most specimens are derived from bone marrow aspirates and thus contain too few cells to evaluate a large panel of drugs; and (2) the colony forming efficiency is so low (usually less than 0.1%) that among those specimens that form colonies in agar, only approximately 20-25% form sufficient colonies to permit detailed analysis of in vitro chemosensitivity. Over the past three years, the development of a selective serum-free hormone-supplemented medium has greatly improved the ability to establish continuous cell lines of SCLC. The biological and biochemical properties of these established cell lines are examined, including: general morphology; growth properties; biochemical markers such as L-dopa decarboxylase (DDC), Bombesin, neuron-specific enolase, and creatine kinase BB; radiation sensitivity; and C-myc oncogene amplification. Among SCLC cell lines, two distinct groups have been identified: classic and variant cell lines. The classic cell lines fail to express the key APUD marker DDC, have a more malignant behavior in vitro, are radioresistant, and are amplified for C-myc DNA. The variant cell lines may be the in vitro model of the mixed small cell/large cell morphological type of SCLC which, in vivo, has a poorer prognosis and survival than pure SCLC. The data generated with SCLC cell lines indicate that SCLC is not a single disease entity but, rather, a morphological spectrum with different behavior and prognosis. (46 Refs)

277. AMPLIFICATION OF THE C-MYC ONCOGENE IN A SUBPOPULATION OF HUMAN SMALL CELL LUNG CANCER

Saksela K, Bergb J, Lehto VP, Nilsson K, Alitalo K
Department of Virology, University of Helsinki, Finland.
Cancer Res; 45(4):1823-7 1985

We have examined a panel of human lung cancer cell lines for amplification and expression of the c-myc, N-myc, and c-myc oncogenes. The cell lines analyzed represent various histopathological types of lung cancer: small cell carcinoma with neuroendocrine properties; squamous cell carcinoma with epithelial markers; and large cell carcinoma with a mixed neuroendocrine-epithelial phenotype. Two of six cell lines, both of which were small cell carcinomas, showed about a 20-fold amplification of the c-myc oncogene. In both cell lines, the amplification is accompanied by an enhanced expression of c-myc. The N-myc or c-myc genes were not

amplified in any of the cell lines, nor were they expressed in detectable amounts. The results confirm and extend earlier findings on c-myc amplification in small cell lung cancer.

278. MOLECULAR AND CYTOLOGIC ANALYSIS OF DNA AMPLIFICATION IN RETINOBLASTOMA

Sakai K, Kanda N, Shibata Y, Denlon T, Schrock R, Shipley J, Dryja T, Chaum E, Chaganti RS, Litt S
Genetics Division, Children's Hospital, Boston, MA 02115.
Cancer Genet Cytogenet; 17(2):95-112 1985

Amplification of two distinct genomic DNA segments is observed in homogeneously staining regions in two sets of retinoblastoma cell lines derived from two different patients. One DNA segment was known to have sequence homology to the c-myc oncogene, and both DNA segments had previously been shown to be amplified in neuroblastoma cells. The absolute degree of amplification differed in all cytogenetically distinct retinoblastoma cell lines tested. Also, the relative amplification of these two DNA segments was unequal within a given cell line. Minimal amplification of both DNA segments was also detected in DNA directly isolated from one primary retinoblastoma. Based on these and previous results, it is concluded that assembly of amplifiable, relocatable units in many human retinoblastoma and neuroblastoma cells may involve a complex process of differential recruitment of separate DNA segments that are located on human chromosome.

279. INCREASED LEVEL OF AMPLIFICATION OF THE C-MYC ONCOGENE IN TUMORS INDUCED IN NUDE MICE BY A HUMAN BREAST CARCINOMA CELL LINE

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Laboratoire d'Oncologie Moléculaire, Institut Gustave Roussy, Villejuif, France.
Cancer Res; 45(9):4372-9 1985

Cell line SW 613-S, derived from a human breast carcinoma, contained double minute chromosomes (DMs) but lost them progressively upon in vitro cultivation. These cells were tumorigenic in nude mice. Cell lines were derived from the tumors and were found to have a high DM content. In three such cell lines, DMs were stably maintained upon in vitro cultivation, whereas in another they were progressively lost. We found that the c-myc oncogene is amplified 5- to 10-fold in SW 613-S and 20- to 90-fold in the different cell lines derived from the tumors. At least part of the additional c-myc copies were found associated with a purified DM fraction. In cell lines which lost the DMs during in vitro passages, the level of amplification was maintained. In situ hybridization experiments indicated that this loss was compensated by the acquisition of copies of the c-myc gene integrated into a chromosome. No major rearrangement of the amplified c-myc gene was detected. The amount of c-myc messenger RNAs is roughly proportional to the level of amplification. Our results indicate that growth of SW 613-S cells as tumors in nude mice selected cells with an increased level of amplification and expression of the c-myc oncogene.

280. AMPLIFICATION OF THE C-MYC ONCOGENE IN HUMAN PLASMA-CELL LEUKEMIA

Sumegi J, Hedberg T, Björkholm M, Gadal T, Mellstedt H, Nilsson MG, Perlman C, Klein G
Department of Tumor Biology, Karolinska Institutet, Stockholm, Sweden.
Int J Cancer; 36(3):367-71 1985

We have examined primary leukemia cells from multiple myeloma and plasma-cell leukemia patients for rearrangement, amplification and expression of c-myc oncogene. No

rearrangement or detectable amplification of the c-myc could be found in 21 cases of multiple myeloma. In contrast, 2/3 cases of plasma-cell leukemia showed amplification of the oncogene with concomitant higher level of expression.

281. ACUTE MYELOGENOUS LEUKAEMIA WITH C-MYC AMPLIFICATION AND DOUBLE MINUTE CHROMOSOMES

Alitalo K, Saksela K, Winqvist R, Alitalo R, Kaiki-Oja J, Laiho M, Ilonen M, Knuutila S, de la Chapelle A
Department of Virology, University of Helsinki, Finland.
Lancet; 2(8463):1035-9 1985

Cytogenetic analysis of bone-marrow cells from a woman with preleukaemia showed numerous mitoses with trisomy 4 and double minute chromosomes. These abnormalities were later seen in blood cells during subsequent acute myeloid leukaemia (AML). Complete remission was achieved with three courses of doxorubicin, cytosine arabinoside, and prednisone. A further clonal abnormality, trisomy 6, was seen in leukaemic cells after the first relapse. Analyses of total DNA from the peripheral-blood cells during relapse showed that the c-myc oncogene was amplified about 30-fold in the leukaemic cells. The N-myc, c-mos, and c-myb oncogenes showed only single-copy signals. On average about two copies of c-myc resided on each dmin chromosome. The finding of amplification of a cellular oncogene (c-myc) in fresh AML cells containing double minute chromosomes suggests that clonal evolution of some leukaemia cell populations may involve selection for increased dosage of oncogenes.

282. AMPLIFICATION AND EXPRESSION OF A CELLULAR ONCOGENE (C-MYC) IN HUMAN GASTRIC ADENOCARCINOMA CELLS

Shibuya M, Yokota J, Uryama Y
Department of Genetics, University of Tokyo, Japan.
Mol Cell Biol; 5(2):414-8 1985

Three of 16 human gastric adenocarcinoma samples, maintained as solid tumors in nude mice, were found to carry amplified c-myc genes. In two samples with a high degree of c-myc DNA amplification (15- to 30-fold), double minute chromosomes were observed in karyotype analysis. The level of c-myc RNA was markedly elevated in a rapidly growing and poorly differentiated tumor, whereas it was only slightly elevated in a slowly growing and more differentiated tumor.

283. C-MYC GENE AMPLIFICATION IN PRIMARY STOMACH CANCER

Koda T, Matsushima S, Sasaki A, Denjo Y, Kakinuma M
Institute of Immunological Science, Hokkaido University, Sapporo.
Jpn J Cancer Res; 76(7):551-4 1985

Fourteen human primary stomach cancer tissues were screened by Southern blot hybridization using six oncogene probes (myc, myb, H-ras, K-ras, abl, mos), and an amplification of c-myc oncogene was found in one tissue. This is the first report of c-onc amplification in primary stomach cancer tissue.

284. AMPLIFICATION AND ALTERED EXPRESSION OF THE C-MYC ONCOGENE IN A-MULV-TRANSFORMED FIBROBLASTS

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Nature; 317(6036):440-3 1985

Chromosomal rearrangements involving the c-myc oncogene are a prevalent feature of plasmacytomas that arise after inoculating BALB/c mice with pristane and Abelson murine leukaemia virus (A-MuLV). With this observation in mind,

we decided to determine if any genetic alterations of the c-myc locus could be observed in cells of a different type, when transformed in vitro by A-MuLV. Here we have analysed three independent A-MuLV-transformed NIH 3T3 lines (ANN-I, 54c12 and N25), and found that the c-myc locus is amplified 8-19-fold in each transformant. Quantitative S1 nuclease mapping performed on ANN-I and 54c12 RNAs demonstrated that: (1) c-myc messenger RNAs accumulated to double the levels found in NIH 3T3 cells; and (2) a shift in the use of the two normal c-myc transcription initiation sites (P1 and P2) occurred in favour of the 3' site. P2. Analysis of c-myc chromatin by DNase I treatment of 54c12 nuclei revealed that most, if not all, of the c-myc gene copies were transcriptionally competent. We present alternative ideas to explain why amplification of the c-myc gene occurs repeatedly in A-MuLV-transformed fibroblasts. Finally, we discuss our results in relation to the hypothesis linking the phenomenon of tumour progression with the amplification of oncogenes.

285. EVOLUTION OF KARYOTYPIC ABNORMALITIES AND C-MYC ONCOGENE AMPLIFICATION IN HUMAN COLONIC CARCINOMA CELL LINES

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Department of Pediatrics, University of Calgary, Alberta, Canada.
Chromosoma; 92(1):11-5 1985

Cell lines (COLO 320 DM and COLO 320 HSR), established from a human neuroendocrine tumor, contain an amplified cellular oncogene (c-myc). We have previously shown that the homogeneously staining regions (HSRs) of a marker chromosome in the COLO 320 HSR cells that evolved in culture from COLO 320 DM cells contain amplified c-myc. Molecular hybridization in situ has now been used to demonstrate that the HSRs are on both arms of what was once an X chromosome. We also show that amplified c-myc copies are present in the isolated double minute chromosomes (DMs) of the COLO 320 DM cells that were characteristic of the tumor cells initially established from the patient. The results suggest that the amplified c-myc appeared first as DMs and was subsequently transposed to engender HSRs on an X chromosome. The initial COLO 320 tumor cell may have acquired two 'early replicating' (i.e., active) X chromosomes and lost the 'late replicating' (i.e., inactive) X.

286. AMPLIFICATION AND ELEVATED EXPRESSION OF C-MYC IN A CHEMICALLY INDUCED MOUSE COLON TUMOR

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Cancer Res; 45(9):4433-8 1985

The amplification and level of expression of four cellular oncogenes was investigated in dimethylhydrazine-induced Mouse Colon Tumor 36 of Corbett et al. [Corbett, T. H. Griswold, D. P., Jr., Roberts, B. J., Peckham, J. C., and Schabel, F. M., Jr. *Cancer* (Phila.), 40:2660-2680, 1977], which has been used to evaluate potential chemotherapeutic agents. A 30- to 40-fold amplification of c-myc was observed in the tumor DNA as compared to the DNA of normal colonic mucosa and liver. No changes were observed in the number of copies of c-mos, erbB, or ras. Digestion with three different restriction enzymes demonstrated that there was no major alteration in the genomic structure of c-myc in the amplified DNA. The level of c-myc RNA was 10-fold higher in both the total and polyadenylated RNA from the tumor when compared to RNA from normal colonic mucosa. Probes specific for the three myc exons were used in hybridization experiments and demonstrated that all three exons were present in the amplified DNA and in the mRNA.

287. AMPLIFICATION AND ENHANCED EXPRESSION OF THE C-MYC ONCOGENE IN MOUSE SEWA TUMOUR CELLS

Schwab M, Ramsay G, Alitalo K, Varmus HE, Bishop JM, Martinsson T, Levan G, Levan A
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Nature; 315(6017):345-7 1985

SEWA tumour cells are derived from an osteosarcoma induced in an A.SW mouse by infection with polyoma virus. Cytogenetic analyses have revealed three different characteristic chromosomal abnormalities diagnostic for the presence of amplified genes: 'double minutes' (DMs), homogeneously staining chromosomal regions (HSRs) and C-banded chromosomes (CMs; for review see ref. 2). DMs may undergo fluctuation in number depending on the conditions in which the cells grow. Their number usually increases after injection of cells into a mouse and often is reduced to undetectable levels when the cells are explanted back into tissue culture; when the cells are re-introduced into the mouse, they again acquire multiple DMs. We show here that cells of SEWA lines carrying DMs, HSRs or CMs contain amplified copies of the proto-oncogene c-myc and enhanced levels of c-myc messenger RNA and c-myc protein. DMs or CMs are the sites of c-myc amplification in two different SEWA lines.

288. ONCOGENE MOBILITY IN A HUMAN LEUKEMIA LINE HL-60

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Cancer Genet Cytogenet; 17(2):133-41 1985

HL-60, a cell line derived from a human promyelocytic leukemia, shows amplification of the oncogene c-myc. Chromosome aberrations reported in HL-60 include double minutes (DMs) and an abnormally banded region (ABR) on chromosome 1. A relationship between these chromosomal aberrations and amplification of c-myc DNA has been suggested. We report the localization by cytologic hybridization of amplified c-myc DNA to a marker chromosome, M3q+, in an early passage of HL-60. The localization of c-myc to an ABR on an 8q+ chromosome was confirmed in later passage clones. The most probable derivation of the M3q+ chromosome is t(5p;17q) with additional material associated with c-myc amplification inserted into 17q. This localization is of interest in light of the association between t(15;17) and promyelocytic leukemia. The results indicate that amplification and chromosome integration can occur at a site other than the native gene locus and at different integration sites in different lineages of the same tumor.

289. PROXIMITY OF THYROGLOBULIN AND C-MYC GENES ON HUMAN CHROMOSOME 8

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Somatic Cell Mol Genet; 11(4):397-402 1985

The human thyroglobulin structural gene (TG) was mapped to the long arm of chromosome 8 by blot hybridization of a TG cDNA probe to DNA from 21 human X mouse somatic cell hybrids containing overlapping subsets of human chromosomes. In situ hybridization of the TG probe to metaphase chromosomes from a karyotypically normal human lymphoblastoid cell line, JS, localized the TG gene to within the region 8q23 - q24.3. Thus, the TG and c-myc genes map to the same chromosome band in normal human cells. In a

human colon carcinoma cell line (COLO 320 DM) which contains amplified c-myc, the TG gene is not amplified and hence it lies outside the amplification domain.

290. EXPRESSION OF C-MYC GENE IN HUMAN HEPATOMA

Su TS, Lin LH, Lui WY, Chang CM, Chou CK, Ting LP, Hu CP, Han SH, P'eng FK
Department of Medical Research, Veterans General Hospital, Taipei, Taiwan, Republic of China.
Biochem Biophys Res Commun; 132(1):264-8 1985

The level of c-myc transcript was examined in liver samples from seven hepatoma patients. Transcripts were detected in all the normal liver parts examined; in contrast, in two hepatoma parts, there was a dramatic reduction in c-myc transcripts. The restriction enzyme pattern of c-myc gene appeared the same among samples. The data suggest that c-myc gene expression might not be required for the maintenance of the tumor state in human liver carcinogenesis.

291. AMPLIFICATION AND OVER-EXPRESSION OF THE C-MYC GENE IN MORRIS HEPATOMAS

Hayashi K, Makino R, Sugimura T
Biochemistry Division, National Cancer Center Research Institute, Tokyo.
Cancer; 75(6):475-8 1984

Morris hepatoma 7794A was found to have its c-myc gene amplified 5- to 10-fold. The over-expression of c-myc was observed in all three hepatomas studied (Morris hepatomas 5123D, 7136A and 7794A), although in the first two instances the c-myc genes were not amplified. Over-expression or de-regulation of c-myc seems to be a general phenomenon associated with hepatoma.

292. AMPLIFICATION, EXPRESSION AND REARRANGEMENT OF C-MYC AND N-MYC ONCOGENES IN HUMAN LUNG CANCER

Nau MM, Carney DN, Battey J, Johnson B, Little C, Gazdar A, Minna JD
Curr Top Microbiol Immunol; 113:172-7 1984

Keywords (MeSH): Base Sequence; Carcinoma, Oat Cell/*familial and genetic; *Gene Amplification; Human; Lung Neoplasms/*familial and genetic; *Oncogenes; Operon; RNA, Messenger/genetics; *Transcription, Genetic; *Translocation (Genetics); Variation (Genetics).

293. EXPRESSION OF THE AMPLIFIED DOMAIN IN HUMAN NEUROBLASTOMA CELLS

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Laboratory of RNA Synthesis and Regulation, Memorial Sloan-Kettering Cancer Center, New York, New York.
Mol Cell Biol; 4(11):2370-80 1984

Screening of a partial cDNA library prepared from the human neuroblastoma cell line BE(2)-C with genomic DNA probes containing sequences representative of the amplified domain of that cell line allowed us to identify cloned transcripts from an active gene within the domain. The gene BE(2)-C-59 is amplified ca. 150-fold and encodes a 3.0- and a 1.5-kilobase RNA transcript, both of which are overproduced in BE(2)-C cells. A survey of a large variety of human tumor cell types indicated that this gene is amplified to varying degrees in all neuroblastoma cell lines and a retinoblastoma cell line that exhibit obvious cytological manifestations of DNA sequence amplification, i.e., homogeneously staining regions and double-minute chromosomes. The BE(2)-C-59 gene is not amplified, however, in other nonrelated tumor types, even those containing amplified DNA. Although the functional significance of this specific gene amplification in neuroblastoma cells remains unknown, an indication that it may

relate to the malignant phenotype of these cells follows from the remainder of our data which show that the amplified BE(2)-C-59 gene shares partial homology with both the second and third exons, but not the first exon, of the human c-myc oncogene.

294. AMPLIFICATION OF THE C-MYC ONCOGENE IN HUMAN STOMACH CANCERS

Nahasato F, Sakamoto H, Mori M, Hayashi K, Shimozato Y, Nishii M, Tahara S, Nakatani K, Terada M, Sugimura T
National Cancer Center Research Institute, Tokyo.
Cancer; 75(9):737-42 1984

Amplified c-myc oncogene was found in the DNAs of 2 of 11 human stomach cancers transplanted into nude mice; the amplification was 8- to 10-fold in one tumor and 13- to 15-fold in the other. Both tumors in which the c-myc oncogene was amplified were poorly differentiated adenocarcinomas, but there was no clear-cut correlation between the histological types or growth rates of the tumors and amplification of the c-myc oncogene. No amplification of the c-myc gene was detected in DNAs from 4 cultured stomach cancer cell lines, 19 primary stomach cancers or 11 metastases to lymph nodes from human stomach cancers.

295. AMPLIFICATION OF THE C-MYC ONCOGENE IN ONE OF FIVE HUMAN BREAST CARCINOMA CELL LINES

Kozbor D, Croce CM
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Cancer Res; 44(2):438-41 1984

The c-myc oncogene was not rearranged in any of five different human breast carcinoma cell lines examined. A 10-fold amplification and an elevated expression of the oncogene were detected in one of these cell lines, and the four other lines expressed low or undetectable levels of c-myc transcripts. Thus, c-myc amplification and elevated expression may be found only in a minority of human breast carcinomas.

296. CELLULAR ONCOGENES: ENHANCEMENT OF THEIR EXPRESSION IN ANIMAL AND HUMAN TUMORS

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Prog Cancer Res Ther; 30:207-18, 1984

To analyze the involvement of endogenous cellular oncogenes in tumorigenesis and transformation, studies were carried out using two different systems, namely, chicken B cell lymphomas induced by avian leukosis virus (ALV) and human lymphoid malignancies such as acute lymphoblastic leukemia, chronic lymphocytic leukemia, and non-Hodgkin's lymphoma. The expression of the chicken cellular oncogene c-myc was found to be enhanced several fold in bursal lymphomas induced by the ALV; integration of the ALV provirus next to the c-myc was considered to activate transcription of the c-myc by providing a strong viral promoter. This mechanism of oncogenesis, called promoter insertion, served as a model for in vivo tumorigenesis by activation of a cellular oncogene. With such a model in mind, samples of peripheral blood leukocytes (PBLs) or lymph nodes were collected from patients (pts) with the different lymphoid malignancies for the purpose of analysis of expression of human sequences homologous to retroviral oncogenes. The analyses were performed on total cellular RNA with the use of either v-myc or chicken c-myc as a probe. Elevated levels of human c-myc transcripts were found in PBLs from some of the pts relative to that in PBLs from normal donors. In addition, evidence

was obtained that HL60, a human promyelocytic leukemia cell line expressing elevated myc transcripts, had an increased copy number of myc DNA sequences. The significance of these results were discussed in relationship to possible mechanisms of oncogenesis.

297. ONCOGENE EXPRESSION IN HUMAN LYMPHOID NEOPLASMS

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Philadelphia, PA 19111
Prog Cancer Res Ther; 27:349-57 1984

The induction of bursal lymphomas (BLs) in chickens by avian leukosis virus (ALV) is presented as an animal model system, the results of which are then related to human lymphoid neoplasms. The ALV's latent period for tumor induction is 4 - 12 mo; the virus sometimes induces sarcomas and nephroblastomas as well as BLs; the tumors resulting from ALV infection are clonal; ALV does not transform cells in culture; and no oncogene has been identified in the genome of ALV. It is postulated that the ALV causes tumors by activating cellular oncogenes. In 30 of 36 ALV-induced BLs, the ALV provirus was found integrated adjacent to the c-myc gene, the cellular homolog of the transforming gene of MC29 virus. ALV inserts were such that transcription initiated by the virus read into the myc sequences. This mechanism is termed 'promoter insertion' and is the first example of tumor formation in which a virus activated the cellular homolog of a viral oncogene. To determine if oncogene expression plays a similar role in human cancer, RNA from peripheral blood lymphocytes and lymphoblasts from 15 patients with primarily B-cell leukemias were analyzed for myc gene expression. Lymphocyte RNA from 9 normal persons was also analyzed. Results indicated that all the normals and 6 of the leukemic patients had very low expression of the myc gene; 9 leukemics showed strong myc gene expression; and one acute lymphoblastic leukemia patient showed expression when in crisis but not when in remission. Expression of myc is apparently associated with the leukemic cells. In leukemic cells where myc was not expressed, it may be that some other oncogene is expressed. Possible mechanisms for genetic change in human cells that could lead to oncogene activation are discussed, including promoter insertion by a retrovirus, inactivation of or mutation in the repressor for the oncogene, a mutation in the regulatory region of the oncogene, gene amplification at the DNA level and demethylation. (21 Refs)

298. GENOMIC ALTERATIONS INVOLVING THE C-MYC PROTO-ONCOGENE LOCUS DURING THE EVOLUTION OF A CASE OF CHRONIC GRANULOCYTIC LEUKAEMIA

McCarthy DM, Russell FV, Goldman JM, Graham SV, Birnie GD
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Hammersmith Hospital, London.
Lancet; 2(8416):1362-5 1984

In a patient with Ph-positive chronic granulocytic leukaemia who had 3 separate episodes of promyelocytic transformation associated with new cytogenetic and genetic changes DNA from the peripheral-blood leucocytes obtained during the second episode of transformation showed an 8-fold to 16-fold amplification of cellular myc proto-oncogene (c-myc) sequences, and rearrangement of these sequences. There was no amplification or rearrangement of c-myc sequences in DNA from leucocytes collected during the chronic phase, nor were these sequences amplified in DNA from leucocytes collected during the third episode of transformation. These observations show that new clones of cells that proliferate

during the evolution of a myeloid leukaemia can carry genetic changes in addition to any recognisable karyotypic changes. Such genetic changes might underlie the progression of the disease.

299. VARIABILITY OF CELL LINES FROM PATIENTS WITH SMALL CELL LUNG CANCER

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20814
Human Tumor Cloning, Fourth Conference on Human Tumor Cloning, Salmon SE, Trent JM, eds. Orlando, Florida, Grune and Stratton, p. 67-81, 1984.

In vitro biological characteristics, radiobiological properties, and results of c-myc oncogene analysis for 52 small-cell lung cancer (SCLC) lines are described and contrasted with non-SCLC lines. Cell lines were established from all sites assayed, including bone marrow, pleural effusions, lymph nodes, and other surgically resected masses. Based on expression of biomarkers, three SCLC subgroups were recognized: (1) classic, (2) variant, and (3) multipotent. Classic cell lines (70% of all lines) grew as tightly-packed aggregates of cells with a relatively prolonged doubling time and a low colony forming efficiency (CFE) in agarose, and formed tumors in nude mice typical of intermediate cell SCLC. Variant cell lines grew as looser aggregates of floating cells, with a faster doubling time, higher CFE, and shorter latent period to tumor formation than classic SCLC lines. X-irradiation of 6 classic and 3 variant SCLC cell lines resulted in similar Do's (51-140 and 80-91, respectively). However, classic cell lines had a low extrapolation number (1-3.3) and fraction of cell surviving 200 R (2-32%) compared to variant cells (5.6-11.1 and 56-50%, respectively). C-myc oncogene analysis was employed with 12 classic SCLC cell lines, 6 variant cell lines, and 3 non-SCLC lung cancer cell lines. Minimal amplification of c-myc DNA (5-fold) was seen in 1/12 of the classic cell lines, whereas a much greater amplification was seen (20-75 fold) in 5/6 of the variant cell lines. The classic cell lines with c-myc amplification gave rise to a variant line after several mo of culture (vide infra); this variant had increased c-myc amplification. One or more homogeneous staining regions were seen in each of 3/3 variant cell lines examined, but in 0/8 of the classic cell lines studied. (36 Refs)

300. PROTEINS ENCODED BY THE HUMAN C-MYC ONCOGENE: DIFFERENTIAL EXPRESSION IN NEOPLASTIC CELLS

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Seattle, Washington.
Mol Cell Biol; 4(11):2486-97 1984

To examine myc protein products in the wide variety of human tumor cells having alterations of the c-myc locus, we have prepared an antiserum against a synthetic peptide corresponding to the predicted C-terminal sequence of the human c-myc protein. This antiserum (anti-hu-myc 12C) specifically precipitated two proteins of 64 and 67 kilodaltons in quantities ranging from low levels in normal fibroblasts to 10-fold-higher levels in Epstein-Barr virus-immortalized and Burkitt's lymphoma cell lines, to 20- to 60-fold-higher levels in cell lines having amplified c-myc. The p64 and p67 proteins were found to be highly related by partial V8 proteolytic mapping, and both were demonstrated to be encoded by the c-myc oncogene, using hybrid-selected translation of myc-specific RNA. In addition, the p64 protein was specifically precipitated from cells transfected with a translocated c-myc gene. Both p64 and p67 were found to be nuclear phosphoproteins with extremely short half-lives. In tumor cell lines having al-

terations at the c-myc locus due to amplification or translocation, we observed a significant change in the expression of p64 relative to p67 when compared with normal or Epstein-Bar virus-immortalized cells.

301. THE PROTEIN ENCODED BY THE HUMAN PROTO-ONCOGENE C-MYC

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California Medical Center, San Francisco.
Proc Natl Acad Sci USA; 81(24):7742-6 1984

The proto-oncogene c-myc may play a role in controlling the growth and division of normal cells, and abnormalities of the gene have been implicated in the genesis of a substantial variety of human tumors. To facilitate further study of these issues, we developed antisera that permit the identification and isolation of the protein encoded by the human and other mammalian versions of c-myc. We found that c-myc(human) gives rise to at least two phosphoproteins with apparent molecular weights of 62,000 [pp62c-myc(human), the major product] and 66,000 [pp66c-myc(human), produced in smaller quantities and possibly a modified version of the Mr 62,000 protein]. Both proteins have relatively short half-lives of approximately equal to 30 min. Mouse c-myc encodes similar proteins with molecular weights of 64,000 and 66,000. The use of cells transformed by DNA-mediated gene transfer sustained previous deductions that the entire coding domain of c-myc(human) is contained in the second and third exons of the gene and resolved previous ambiguities by showing that analogous exons specify the entire protein product of c-myc(chicken). Tumor cells containing amplification of c-myc(human) produce relatively large amounts of pp62/pp66c-myc(human). By contrast, translocations of c-myc found in cells derived from Burkitt lymphoma appear merely to sustain expression of c-myc(human) at levels found also in nontumorigenic lymphoblastoid cells, rather than to increase expression of the gene to manifestly abnormal levels.

302. ASSOCIATION OF AMPLIFIED ONCOGENE C-MYC WITH AN ABNORMALLY BANDED CHROMOSOME IN A HUMAN LEUKAEMIA CELL LINE

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Nature; 306(5942):494-7 1983

Several unusual chromosome structures have been described in drug-resistant cell lines and in certain tumours. These structures include elongated homogeneously staining regions (HSRs), small extrachromosomal paired chromatin bodies (double minutes, DMs) and abnormally banded regions (ABRs) with strong but anomalous band patterns. There is evidence that these are alternative forms of gene amplification, with HSRs breaking down to form DMs, and DMs integrating into the chromosome to generate HSRs and ABRs. Recently, it was demonstrated that, compared with several normal and leukaemia human cells, DNA sequences representing the human homologue of the onc gene of the avian myelocytomatosis virus (MC29), the so-called c-myc gene, were amplified in HL-60 cells. This is a human promyelocytic leukaemia cell line established in the laboratory of one of us (R.C.G.) at the National Cancer Institute (Bethesda, Maryland) in 1977, and widely used for studies on myeloid and monocytic differentiation. Amplification of the gene was present in primary leukaemic cells of the patient, and DMs were noted in some of these cells as well as in early passages of the HL-60 line. No structure resembling HSRs or ABRs were noted in karyotypic studies at this early stage and there were no alterations involving the long arm of chromosome 8

(8q), to which the c-myc gene has recently been mapped. We have now re-examined the karyotype of the HL-60 line, using cells frozen at various times during its continuous passage at the Wistar Institute (Philadelphia, Pennsylvania) to look for chromosomal abnormalities that might be associated with the amplification of c-myc. We find that, beginning in 1979, HL-60 cells at the Wistar Institute no longer had DMs, but did show an abnormal 8q+ chromosome, replacing a normal chromosome 8, and representing an ABR reflecting the site of myc gene amplification.

303. AMPLIFICATION AND EXPRESSION OF THE C-MYC ONCOGENE IN HUMAN LUNG CANCER CELL LINES

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Nature; 306(5939):194-6 1983

Genetic changes involving the c-myc oncogene have been observed in human tumours. In particular, the c-myc gene is translocated in Burkitt's lymphoma and is amplified in the human promyelocytic leukaemia cell line, HL-60, which contains double minute chromosomes (DMs). More recently, an amplified c-myc gene has been positioned on a chromosomal homogeneously staining region (HSR) in a human colon cancer cell line, COLO 320, with neuroendocrine properties. Furthermore, c-myc is expressed in increased amounts in some human tumour lines, and in some cases, human small cell lung cancers (SCLC) contain DMs and HSRs. These findings prompted us to study the c-myc gene and its RNA expression in a series of human lung cancer cell lines. We now report amplification and expression of the c-myc oncogene in a system other than B-cell lymphomas, namely human lung cancer. Of 18 human lung cancer cell lines tested, 8 showed an amplified 12.5-kilobase (kb) EcoRI c-myc DNA band. Of particular interest are five SCLC lines with a high degree of c-myc DNA amplification (20-76-fold) and greatly increased levels of c-myc RNA. All five lines reside in the variant class of SCLC (SCLC-V) characterized by altered morphology, lack of expression of some SCLC-differentiated functions and more malignant behaviour than pure SCLC. Three of the five lines which have been karyotyped also contain DMs or HSRs. The finding of a greatly amplified c-myc gene in all cell lines of the SCLC-V class examined strongly suggests a role for the c-myc gene in the phenotypic conversion and malignant behaviour of human lung cancer.

304. AMPLIFIED DNA WITH LIMITED HOMOLOGY TO MYC CELLULAR ONCOGENE IS SHARED BY HUMAN NEUROBLASTOMA CELL LINES AND A NEUROBLASTOMA TUMOUR

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Nature; 305(5931):245-8 1983

Amplified cellular genes in mammalian cells frequently manifest themselves as double minute chromosomes (DMs) and homogeneously staining regions of chromosomes (HSRs). With few exceptions both karyotypic abnormalities appear to be confined to tumour cells. All vertebrates possess a set of cellular genes homologous to the transforming genes of RNA tumour viruses, and there is circumstantial evidence that these cellular oncogenes are involved in tumorigenesis. We have recently shown that DMs and HSRs in cells of the mouse adrenocortical tumour Y1 and an HSR in the human colon carcinoma COLO320 contain amplified copies of the cellular oncogenes c-Ki-ras and c-myc, respectively. Both

DMs and HSRs are found with remarkable frequency in cells of human neuroblastomas. We show here that a DNA domain detectable by partial homology to the myc oncogene is amplified up to 140-fold in cell lines derived from different human neuroblastomas and in a neuroblastoma tumour, but not in other tumour cells showing cytological evidence for gene amplification. By in situ hybridization we found that HSRs are the chromosomal sites of the amplified DNA. The frequency with which this amplification appears in cells from neuroblastomas and its apparent specificity raise the possibility that one or more of the genes contained within the amplified domain contribute to tumorigenesis.

305. IDENTIFICATION AND NUCLEOTIDE SEQUENCE OF A HUMAN LOCUS HOMOLOGOUS TO THE V-MYC ONCOGENE OF AVIAN MYELOCYTOMATOSIS VIRUS MC29

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Nature; 301(5904):722-5 1983

Avian myelocytomatosis virus MC29 is a replication-defective acute leukaemia virus which induces a variety of tumours in chickens including sarcomas, renal and hepatic carcinomas, and myelocytomatosis. The oncogenic potential of the virus is mediated by the gene v-myc, acquired from sequences (c-myc) present in normal uninfected chicken DNA. Sequences closely related to chicken c-myc have been highly conserved throughout evolution, from *Drosophila* to vertebrates. The hypothesis that c-myc may be involved in neoplastic transformation has been strengthened by the finding that B-cell lymphomas induced in chickens by avian leukosis virus (ALV) are often associated with increased expression of c-myc resulting from integration of the ALV provirus adjacent to the c-myc gene. More recently, it has been demonstrated that the malignant human cell line HL-60, derived from the peripheral blood leukocytes of a patient with acute promyelocytic leukaemia, expresses elevated levels of myc-related mRNA associated with an amplification of the c-myc gene. To explore the relationship of the human cellular myc gene with the corresponding viral oncogene from MC29, and to provide a framework for the analysis of the mechanism and significance of c-myc amplification in human tumours, we have isolated and determined the nucleotide sequence of a genomic clone prepared from a normal human library which contains all domains sharing homology with v-myc.

306. HOMOGENEOUSLY STAINING CHROMOSOMAL REGIONS CONTAIN AMPLIFIED COPIES OF AN ABUNDANTLY EXPRESSED CELLULAR ONCOGENE (C-MYC) IN MALIGNANT NEUROENDOCRINE CELLS FROM A HUMAN COLON CARCINOMA

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Proc Natl Acad Sci USA; 80(6):1707-1711 1983

Two human neuroendocrine tumor cell lines derived from a colon carcinoma contain either numerous double minute chromosomes (COLO 320 DM) or a homogeneously staining marker chromosome (COLO 320 HSR). We found amplification and enhanced expression of the cellular oncogene c-myc in both COLO 320 DM and HSR cells, and we were able to show that the homogeneously staining regions of the COLO 320 HSR marker chromosome contain amplified c-myc. From previous and present karyotypes, it appears that the homogeneously staining regions reside on a distorted X chromosome. Therefore, amplification of c-myc has been accompanied by translocation of the gene from its normal position on chromosome 8 (8q24). Because double minute chromosomes

were features of primary cultures from the original tumor, it seems reasonable to suspect that amplification of c-myc may have contributed to tumorigenesis. (Author abstract) (40 Refs)

307. AMPLIFICATION OF ENDOGENOUS MYC-RELATED DNA SEQUENCES IN A HUMAN MYELOID LEUKAEMIA CELL LINE

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Nature; 298(5874):679-681 1982

Multiple copies of sequences in normal human DNA homologous to the avian myc oncogene were demonstrated in the chromosomal DNA of the human leukemia cell line HL-60 obtained from a patient with acute promyelocytic leukemia. Enhanced hybridization of the c-myc probe to HL-60 DNA was observed which did not result from technical considerations. The intensity of hybridization was comparable to that noted in DNA extracted from normal avian cells and from avian cells infected with the acute transforming MH2 virus, a MC-29 avian retrovirus. However, the hybridization between HL-60 DNA and the c-myc probe did not seem to result from inadvertent infection of HL-60 cells with a retrovirus. Restriction enzyme patterns of HL-60 and normal human DNA hybridized to c-myc were similar indicating that HL-60 and normal human myc-related DNA sequences are similar. Enhanced hybridization of the c-myc probe to HL-60 DNA seemed to result from HL-60 amplification of endogenous human myc-related sequences rather than from increased homology of the sequences to the c-myc probe. The c-myc-related sequences were amplified 8-16-fold in HL-60 DNA compared with normal human DNA. Other transformation-specific genes derived from the Abelson leukemia virus and feline sarcoma virus were not amplified in HL-60. The myc-related gene amplification was not present in other cultured human myeloid leukemia cells, including K-562 leukemia and KG-1 cells. (30 Refs)

308. ONC GENE AMPLIFICATION IN PROMYELOCYTIC LEUKAEMIA CELL LINE HL-60 AND PRIMARY LEUKAEMIC CELLS OF THE SAME PATIENT

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Nature; 299(5877):61-63 1982

Amplification of oncogenes in cells from a patient with acute promyelocytic leukemia (APL) was studied. The structure of c-myc, a cellular homolog of the transforming gene of avian myelocytomatosis virus (MC29) was studied by means of Southern blot hybridization. DNA was obtained from HL-60 cells derived from the APL patient, primary leukemic cells from the same patient, from normal human tissues, and various neoplastic tissues. The neoplastic cells included peripheral blood cells from patients with acute myelogenous leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, acute myelomonoblastic leukemia, and cell lines derived from different leukemias. Except for the HL-60 cells and the primary cells from the APL patient, all samples showed the same intensity of the 2.8 kilobase (kb) band of DNA. The HL-60 and primary APL cells showed a strong increase in the 2.8 kb DNA. Similar results were obtained with different passages of HL-60 cells and after induction of differentiation of HL-60 cells with dimethylsulfoxide. HL-60 cells showed a decrease in 12.8 kb DNA; the intensity of 5.8 kb DNA was uniform in all samples. Apparently the functional gene, but not related sequences, were amplified in HL-60 cells. HL-60 cells also contained 4.6 kb DNA not found in other cells; this DNA may be a pseudogene. The c-

myc gene was amplified in HL-60 and primary APL cells by a factor of 16-32. Whether the c-myc is amplified in nonleukemic cells from the APL patient is unknown. (28 Refs)

2.

Amplification of N-myc and I-myc Oncogenes

309. HUMAN SMALL-CELL LUNG CANCERS SHOW AMPLIFICATION AND EXPRESSION OF THE N-MYC GENE

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Proc Natl Acad Sci USA; 83(4):1092-6 1986

We have found that 6 of 31 independently derived human small-cell lung cancer (SCLC) cell lines have 5- to 170-fold amplified N-myc gene sequences. The amplification is seen with probes from two separate exons of N-myc, which are homologous to either the second or the third exon of the c-myc gene. Amplified N-myc sequences were found in a tumor cell line started prior to chemotherapy, in SCLC tumor samples harvested directly from tumor metastases at autopsy, and from a resected primary lung cancer. Several N-myc-amplified tumor cell lines also exhibited N-myc hybridizing fragments not in the germ-line position. In one patient's tumor, an additional amplified N-myc DNA fragment was observed and this fragment was heterogeneously distributed in liver metastases. In contrast to SCLC with neuroendocrine properties, no non-small-cell lung cancer lines examined were found to have N-myc amplification. Fragments encoding two N-myc exons also detect increased amounts of a 3.1-kilobase N-myc mRNA in N-myc-amplified SCLC lines and in one cell line that does not show N-myc gene amplification. Both DNA and RNA hybridization experiments show that in any one SCLC cell line, only one myc-related gene is amplified and expressed. We conclude that N-myc amplification is both common and potentially significant in the tumorigenesis or tumor progression of SCLC.

310. AMPLIFICATION UNITS CONTAINING HUMAN N-MYC AND C-MYC GENES

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Proc Natl Acad Sci USA; 83(4):1031-5 1986

The amplification units in human tumors containing amplified myc genes were examined. The amplification unit in all cases consisted of a large genomic region coamplified with the coding region of the myc genes themselves. In eight independent neuroblastomas containing N-myc amplifications, the amplification unit was estimated to be 290 to 430 kilobases. This amplification unit was highly conserved among the different neuroblastomas, with some neuroblastomas containing almost identical units. In contrast, five tumor cell lines containing c-myc amplifications exhibited amplification units that were more variable in size (90 to 300 kilobases) and sequence content; at least three different patterns of c-myc amplification units could be discerned.

311. [ONCOGENE AMPLIFICATION IN HUMAN NEUROBLASTOMAS]

Kanda N, Tsurubida Y, Hayashi Y, Ise T, Takayama J, Utsukiji T
Tokyo Women's Medical College.
Gan To Kagaku Ryobo; 13(3 Pt 2):661-6 1986

N-myc, which has partial sequence homology to the oncogene c-myc, was isolated from human neuroblastoma cell lines. We have surveyed amplification of N-myc, clone 8 and

pG21 in human neuroblastoma cell lines, xenografts and in primary tumors and found that amplification frequently occurred in tumors classified as stage III and IV. In situ hybridization studies demonstrated that in neuroblastomas, chromosome aberrations such as HSR (homogeneously staining region) and DMs (double minutes) are cytological manifestations of the amplification of these clones. The N-myc-related gene seems to contribute to cell growth or differentiation of the nerve cell and its amplification with enhanced expression promotes the progression of the tumor with poor prognosis.

312. GENE AMPLIFICATION IN HUMAN NEUROBLASTOMAS: BASIC MECHANISMS AND CLINICAL IMPLICATIONS

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Cancer Genet Cytogenet; 19(1-2):101-11 1986

Extrachromosomal double minutes (DM) and homogeneously staining regions (HSR) of metaphase chromosomes have been reported frequently in human neuroblastomas and tumor derived cell lines. We and other investigators have determined that virtually all DM- and HSR-bearing neuroblastoma cell lines have multiple copies of the oncogene N-myc. Circumstantial evidence suggests that the extrachromosomal DM may be the level at which amplification takes place, with subsequent linear integration into HSR. Indeed, DM may represent circular molecules. The global organization and fine structure of the amplified sequences remains to be determined, but the unit of amplification is probably between 2 X 10(5) and 2 X 10(6) base pairs (bp). In some cases, the process of amplification may involve somatic recombination with distant DNA segments. We have determined that N-myc amplification is a common finding in primary neuroblastomas from untreated patients. We identified N-myc amplification, ranging from 3- to 300-fold, in 34 of 89 cases (38%). N-myc amplification is found almost exclusively in tumors from patients with advanced stages of disease (stages III and IV, p less than 0.01). In addition, the presence of amplification is highly correlated with rapid tumor progression (p less than 0.001). Thus, amplification of the N-myc oncogene is a new intrastage prognostic factor, and N-myc amplification appears to play an important role in determining disease progression.

313. DIFFERENTIAL AMPLIFICATION, ASSEMBLY, AND RELOCATION OF MULTIPLE DNA SEQUENCES IN HUMAN NEUROBLASTOMAS AND NEUROBLASTOMA CELL LINES

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Proc Natl Acad Sci USA; 82(11):3761-5 1985

DNA amplification, manifested by homogeneously staining regions in chromosomes and by extrachromosomal, double minute bodies, is characteristic of many neuroblastoma cell lines. Sequences recruited from a specific domain on the short arm of chromosome 2 (2p) are amplified in advanced-stage primary neuroblastomas, whereas sequences from distinctly different regions of 2p are amplified in the neuroblastoma cell line IMR-32. Five different DNA segments, which include the oncogene N-myc, three other fragments derived from the homogeneously staining region of the neuroblastoma cell line IMR-32, and a fifth fragment, derived from the neuroblastoma cell line NB-9, showed differential and variable amplification in 24 advanced-stage neuroblastoma tumors out of 112 tested specimens. All five fragments were mapped within the chromosomal region 2p23-2p25 by three different approaches. However, eight other fragments cloned

from the homogeneously staining region of IMR-32 cells, which were not amplified in the tumor tissues examined, were mapped to two more proximal domains of 2p, thousands of kilobases apart from each other and from the chromosomal domain that is amplified in the tumors. These results establish the amplification, to different degrees, of a variable-sized segment of one domain near the terminus of 2p in advanced neuroblastomas. These tumors might ultimately be distinguished according to the pattern of amplification of DNA segments within this domain. The data presented also indicate the existence of a new and complex amplification mechanism in at least one neuroblastoma cell line (IMR-32), which involves not only relocation of DNA from specific genomic domains but also the formation of novel units by splicing together very distant DNA segments.

314. HUMAN N-MYC GENE CONTRIBUTES TO NEOPLASTIC TRANSFORMATION OF MAMMALIAN CELLS IN CULTURE

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Nature; 316(6024):160-2 1985

Proto-oncogenes represent a group of eukaryotic genes whose activated forms are implicated in the development of cancer. We have recently identified a human gene, N-myc, that is distantly related to the proto-oncogene c-myc. N-myc is expressed at abnormally high levels consequent to amplification in numerous human neuroblastoma cell lines and metastatic neuroblastoma tumours. In addition, enhanced expression of N-myc, often a result of amplification, has been found in retinoblastoma cell lines and tumours (refs 5, 7 and M.S., unpublished data) and in cell lines derived from small-cell carcinomas of the lung. Here, we show that enhanced expression of N-myc subsequent to co-transfections of an N-myc expression vector and the mutant c-Ha-ras-1(EJ) (from the human bladder carcinoma cell line EJ) is a factor in tumorigenic conversion of secondary rat embryo cells. The transformed cells elicit tumours in athymic mice and isogenic rats. The ability of N-myc to contribute to neoplastic transformation of cultured mammalian cells raises the possibility that enhanced expression consequent to amplification of N-myc may be a factor in the aetiology of human neuroblastoma.

315. AMPLIFICATION OF N-MYC SEQUENCES IN PRIMARY HUMAN NEUROBLASTOMAS: CORRELATION WITH ADVANCED DISEASE STAGE

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Proc Clin Biol Res; 175:105-13 1985

Keywords (MeSH): Child; Child, Preschool; DNA, Neoplasm/genetics; *Gene Amplification; Human; Infant; Neoplasm Staging; Neuroblastoma/*familial and genetic/pathology; *Oncogenes.

316. AMPLIFIED DNA SEQUENCES IN CANCERS

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Biochem Biophys Res Commun; 130(2):508-14 1985

Amplification of genes other than known oncogenes was analyzed using an in-gel DNA renaturation method, in which a mixture of restriction fragments of radioactively labelled tracer DNA and unlabelled driver DNA was electrophoresed and amplified DNA fragments were visualized after two cycles of denaturation and renaturation in the gel. Different DNA fragments were found to be amplified more than 400 fold in NB1, a neuroblastoma cell line, in Y79, a retinoblas-

toma cell line and in H69, a small cell lung carcinoma cell line, in addition to 120 to 160-fold amplification of N-myc gene in these three cell lines.

317. RETINOIC ACID TREATMENT OF HUMAN NEUROBLASTOMA CELLS IS ASSOCIATED WITH DECREASED N-MYC EXPRESSION

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Biochem Biophys Res Commun; 126(3):1189-95 1985

Cells from human neuroectodermal tumors (retinoblastoma and neuroblastoma) and from neuroblastoma cell lines express a gene, N-myc, which is frequently amplified in these tumors. We report here that N-myc mRNA content is markedly decreased in cells of a neuroblastoma cell line (LA-N-5) following differentiation induced with retinoic acid. Exposure of the cells to retinoic acid induced morphologic changes consistent with neuronal differentiation, and led to a 75% decrease in expression of N-myc mRNA. These results suggest that N-myc expression is intimately related to an undifferentiated phenotype in neuroblastoma cells, and support other studies which relate N-myc expression to the malignant phenotype in neuroblastoma tumors.

318. DECREASED EXPRESSION OF N-MYC PRECEDES RETINOIC ACID-INDUCED MORPHOLOGICAL DIFFERENTIATION OF HUMAN NEUROBLASTOMA

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Nature; 313(6001):404-6 1985

Proto-oncogenes may be important in the cellular processes central for the growth and differentiation of normal cells. N-myc is a DNA sequence which shares limited homology to the proto-oncogene c-myc and has been found to be amplified in both primary tissue and cell lines from neuroblastoma, a childhood tumour of neuroectodermal origin. Differentiation of this embryonal tumour is of clinical importance, since occasional tumours have been noted to differentiate in vivo to benign ganglioneuroma. In vitro, many human neuroblastoma cell lines can be induced to differentiate morphologically and biochemically by a variety of agents. Retinoic acid (RA), an analogue of vitamin A, has been shown to inhibit neuroblastoma cell growth and clonability in soft agar, and to induce extensive neurite outgrowth. Therefore we examined the relationship of N-myc expression to the in vitro differentiation of these cells. We report here that in the case of RA-induced differentiation, a decreased level of expression is detected within 6 h of treatment and precedes both cell-cycle changes and morphological differentiation.

319. N-MYC AMPLIFICATION IN MULTIPLE HOMOGENEOUSLY STAINING REGIONS IN TWO HUMAN NEUROBLASTOMAS

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Proc Natl Acad Sci USA; 82(11):3736-40 1985

Molecular characterization of two human neuroblastoma cell lines has revealed that both contain multiple homogeneously staining regions (HSRs), each representing a chromosome site of N-myc amplification. The newly established cell line CHP-382/JK had two cytogenetically distinct populations with several identical chromosomal abnormalities, indicating a common progenitor cell. Each population had one HSR, one on chromosome 5 at q31-34 and the other on chromosome 2 at q31-32. Chromosomal in situ hybridization with the

N-myc probe pNb-1 demonstrated that both HSRs contained amplified copies of N-myc. Southern blot analysis confirmed amplification of N-myc sequences in genomic DNA of CHP-382/JK. Chromosomal features of CHP-382/JK shared with other neuroblastoma cell lines were the deletion of 1p and the presence of extra 17q material. In addition, the cells were highly reactive to monoclonal antibody PI 153/3 used to identify human neuroblastoma. CHP-382/JK cells were further characterized as neuronal cells by the expression of neurotoxin-responsive Na⁺ channels. Another neuroblastoma cell line, CHP-134, contained a single cell population with three HSRs, one in the short arm of each chromosome 7 and one in the long arm of a chromosome 6. All three HSRs contained amplified copies of N-myc as shown by in situ hybridization with the N-myc probe pNb-1. One of the 7p HSRs was acquired during culture of CHP-134 cells, whereas the 2q HSR of CHP-382/JK was lost. Such findings highlight the continued process of N-myc amplification and transposition in vitro. To our knowledge, amplification of N-myc in multiple HSRs has not been documented previously in neuroblastoma cell lines.

320. ASSOCIATION OF MULTIPLE COPIES OF THE N-MYC ONCOGENE WITH RAPID PROGRESSION OF NEUROBLASTOMAS

Seeger RC, Brodeur GM, Sather H, Dalton A, Siegel SE, Wong KY, Hammond D
Children's Cancer Study Group, Los Angeles, CA.
N Engl J Med; 313(18):1111-6 1985

Eighty-nine patients with untreated primary neuroblastomas were studied to determine the relation between the number of copies of the N-myc oncogene and survival without disease progression. Genomic amplification (3 to 300 copies) of N-myc was detected in 2 of 16 tumors in Stage II, 13 of 20 in Stage III, and 19 of 40 in Stage IV; in contrast, 8 Stage I and 5 Stage IV-S tumors all had 1 copy of the gene (P less than 0.01). Analysis of progression-free survival in all patients revealed that amplification of N-myc was associated with the worst prognosis (P less than 0.0001); the estimated progression-free survival at 18 months was 70 per cent, 30 per cent, and 5 per cent for patients whose tumors had 1, 3 to 10, or more than 10 N-myc copies, respectively. Of 16 Stage II tumors, 2 with amplification metastasized, whereas only 1 of 14 without amplification did so (P = 0.03). Stage IV tumors with amplification progressed most rapidly: nine months after diagnosis the estimated progression-free survival was 61 per cent, 47 per cent, and 0 per cent in patients whose tumors had 1, 3 to 10, or more than 10 copies, respectively (P less than 0.0001). These results suggest that genomic amplification of N-myc may have a key role in determining the aggressiveness of neuroblastomas.

321. N-MYC CAN COOPERATE WITH RAS TO TRANSFORM NORMAL CELLS IN CULTURE

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Proc Natl Acad Sci USA; 82(16):5455-9 1985

N-myc, a cellular gene bearing homology to the c-myc protooncogene, is frequently amplified and overexpressed in a highly restricted set of related tumors, most notably neuroblastomas and retinoblastomas. We have examined the possibility that N-myc may play a causal role in the genesis of these tumors by defining its ability to transform primary cells in tissue culture. Using an N-myc expression construct capable of producing constitutively deregulated levels of full-length murine N-myc mRNA, we demonstrate that a deregulated N-myc gene can cooperate with the activated Ha-

ras oncogene to cause tumorigenic conversion of normal embryonic fibroblasts in a manner indistinguishable from the deregulated c-myc oncogene. Cell lines established from N-myc/ras-transformed foci express high levels of the N-myc gene, and such lines are similar to c-myc/ras transformants in their ability to grow in soft agar and cause tumors in syngeneic rats. These results illustrate that N-myc does encode a c-myc-like transforming activity and that this transforming activity is not specific for the very restricted set of tumors in which N-myc is normally amplified or overexpressed.

322. EXPRESSION OF N-MYC IN TERATOCARCINOMA STEM CELLS AND MOUSE EMBRYOS

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Nature; 318(6042):188-91 1985

The N-myc gene, which is distantly related to the proto-oncogene c-myc, was first detected as an amplified sequence in human neuroblastoma cell lines and tumours. It has since been revealed that there is up to a 300-fold amplification of N-myc DNA in almost 50% of advanced metastatic human neuroblastomas, whereas amplification is not detected in less advanced tumours that have a better prognosis (ref.3 and M.S., unpublished data). Although expression of N-myc is detectable in all neuroblastoma cell lines and tumours examined, its level is greatly enhanced when the N-myc gene is amplified. Recently, it has been shown that on co-transfection with the c-Ha-ras (EJ) gene, N-myc can induce the malignant transformation of rat embryo fibroblasts. Taken together, these data imply a function for N-myc in the development and/or progression of human neuroblastomas. Surveys indicate that N-myc also may be amplified and/or expressed in two other types of human tumours and cell lines derived from them: retinoblastomas and small cell lung cancers. Here, we report that N-myc is expressed at high levels in mouse and human teratocarcinoma stem cells, thus identifying another tumour cell type that expresses the N-myc gene. In addition, we found that N-myc is abundantly expressed in mouse embryos at mid-gestation and that its expression appears to decrease as the embryo approaches term. In the adult mouse, N-myc is expressed at an approximately fivefold lower level in the brain than in teratocarcinoma stem cells and embryos, and at even lower levels in the adult testis and kidney. Our data represent the first demonstration of expression of the N-myc gene in normal cells, and suggest that N-myc may be involved in mammalian embryogenesis.

323. NUCLEOTIDE SEQUENCE OF THE 3' EXON OF THE HUMAN N-MYC GENE

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Nucleic Acids Res; 13(7):2545-58 1985

We have analyzed a 3.8 kb Eco RI fragment of genomic DNA obtained from the amplified N-myc gene of human neuroblastoma cell line BE(2)-C. This fragment contains an exon with an open reading frame encoding approximately 170 amino acids of the carboxy-terminal end of the putative N-myc protein. Comparison of the inferred amino acid sequence of this peptide with that of the 3' domain of the human c-myc protein shows that locally conserved but dispersed regions of homology exist throughout the lengths of these peptides, while hydropathy plots indicate that the physical properties implied by their primary sequences are strikingly similar. Based upon these and other considerations, it is suggested that the 3' domains of c-myc and N-myc may potentially share related functions.

324. ACTIVATED EXPRESSION OF THE N-MYC GENE IN HUMAN NEUROBLASTOMAS AND RELATED TUMORS

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Science; 226(4680):1335-7 1984

In neuroblastoma lines in which the N-myc gene is present as a single copy, the expression of N-myc as messenger RNA is increased relative to that in nonneuroblastoma cell lines and tumors. The increase of expression in neuroblastomas with amplified N-myc genes is the result of (i) an increase in the absolute amount of expression of each N-myc gene and (ii) an increase in the copy number of the N-myc gene. A second gene - which is amplified in many of the same lines as N-myc - is expressed to about the same degree in most human cell lines and primary tumors regardless of origin (when normalized to gene copy number). Thus, a change in the regulation of N-myc expression in neuroblastomas and certain other tumors results in greatly increased expression of each N-myc gene copy.

325. ENHANCED EXPRESSION OF THE HUMAN GENE N-MYC CONSEQUENT TO AMPLIFICATION OF DNA MAY CONTRIBUTE TO MALIGNANT PROGRESSION OF NEUROBLASTOMA

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G. W. Hooper Foundation, San Francisco, CA.
Proc Natl Acad Sci USA; 81(15):4940-4 1984

Previous studies had revealed that DNA with partial similarity to the myc oncogene (N-myc) is frequently amplified in human neuroblastoma cell lines and neuroblastoma tumors. We show here for one patient that N-myc amplification is confined to the neuroblastoma tumor and is not present in normal tissue. N-myc mRNA approximately equal to 4.0 kilobases in size is detectable in neuroblastoma cell lines and tumors and in a retinoblastoma cell line. By contrast, appreciable amounts of this RNA were not present in a number of cell lines derived from other human tumors and in fibroblasts from a normal individual and from a neuroblastoma patient. Low levels of N-myc RNA were found in human and murine neuroblastoma cell lines lacking amplification of this gene, up to 80-fold greater levels in all cell lines carrying amplified N-myc. In situ hybridization to sections of neuroblastoma tumors revealed high expression of N-myc predominantly in undifferentiated neuroblasts. We hypothesize that amplification and consequent elevated expression of N-myc may be related to malignant progression.

326. AMPLIFICATION OF N-MYC IN UNTREATED HUMAN NEUROBLASTOMAS CORRELATES WITH ADVANCED DISEASE STAGE

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Science; 224(4653):1121-4 1984

A domain of DNA designated N-myc is amplified 20- to 140-fold in human neuroblastoma cell lines but not in cell lines from other tumor types. N-myc has now been found to be amplified in neuroblastoma tissue from 24 of 63 untreated patients (38 percent). The extent of amplification appears to be bimodal, with amplification of 100- to 300-fold in 12 cases and 3- to 10-fold in 10 others. Amplification was found in 0 of 15 patients with stage 1 or 2 disease, whereas 24 of 48 cases (50 percent) with stage 3 or 4 had evidence of N-myc amplification. These data indicate that N-myc amplification is a common event in untreated human neuroblastomas. Furthermore, N-myc amplification is highly correlated with ad-

vanced stages of disease (P less than 0.001) and with the ability to grow in vitro as an established cell line, both of which are associated with a poor prognosis.

327. EXPRESSION AND AMPLIFICATION OF THE N-MYC GENE IN PRIMARY RETINOBLASTOMA

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Nature; 309(5967):458-60 1984

Retinoblastoma, the most common intraocular tumour of childhood, probably arises from embryonal cells and occurs in hereditary and non-hereditary forms. Recent evidence suggests that this retinoblastoma (Rb) susceptibility gene located at chromosome 13q14 is actually recessive. Knudson has proposed that the tumour is caused by two mutational events. This idea was extended by Comings, who suggested that dominantly inherited tumours may result from loss or inactivation of both alleles of regulatory or suppressor genes that, when active, prevent the expression of a structural transforming gene(s) (possibly an oncogene) normally active only during embryogenesis. Despite circumstantial evidence for this hypothesis, no activated oncogene has been identified. We now report that (1) the N-myc gene is amplified 10-200-fold in two primary retinoblastomas and a retinoblastoma cell line Y79 and (2) expression of N-myc gene is highly elevated in most of the retinoblastomas examined. This finding suggests that N-myc gene may have a primary role in the tumorigenesis of retinoblastoma.

328. CHROMOSOME LOCALIZATION IN NORMAL HUMAN CELLS AND NEUROBLASTOMAS OF A GENE RELATED TO C-MYC

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Nature; 308(5956):288-91 1984

Cellular oncogenes comprise a class of genes whose aberrant expression or function may be involved in the development of tumours. Indeed, several naturally occurring animal and human tumours are associated with consistent alterations in the structure or genomic position of particular cellular oncogenes. Recently, we isolated a DNA segment having limited similarity to c-myc (termed N-myc) from a human neuroblastoma cell line. Although N-myc was present as a single copy in normal cells, it was selectively amplified up to 140-fold in tumour cells from human neuroblastomas. Now, we have used somatic cell hybrids to show that N-myc is normally localized on the distal short arm of chromosome 2, and in situ hybridization to localize N-myc to chromosome 2p23-24. Further, in situ hybridization localizes amplified N-myc in neuroblastoma cells to homogeneously staining regions (HSRs) on different chromosomes. Thus, our results suggest that amplification and translocation of N-myc may be interrelated processes associated with human neuroblastoma, and demonstrate that the site of N-myc amplification is quite variable and bears no apparent relationship to either the normal single-copy locus or recognized sites of non-random chromosome alteration in human neuroblastoma.

329. TRANSPOSITION AND AMPLIFICATION OF ONCOGENE-RELATED SEQUENCES IN HUMAN NEUROBLASTOMAS

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Cell, 35(2 Pt 1):359-67 1983

We have cloned a 2.0-kb EcoRI fragment of human genomic DNA (NB-19-21) which has homology to the v-myc oncogene but is distinct from the classical c-myc gene. This sequence is amplified from 25- to 700-fold in eight of nine tested human neuroblastoma cell lines which contain either homogeneously staining regions or double minutes (HSRs or DMs), the cytological manifestations of amplified genes. In the remaining line, the c-myc proto-oncogene is amplified approximately 30-fold. NB-19-21 hybridizes to a 3.2-kb cytoplasmic, poly(A)+ RNA species that is abundant only in lines in which the sequence is amplified. We propose that the gene encoding the NB-19-21-related RNA species may represent a new oncogene, which we call N-myc. NB-19-21 derives from chromosome 2; but in the five HSR-containing lines that have amplified this sequence, none has HSRs on chromosome 2. NB-19-21 is associated with DMs in a DM-containing line. A second, randomly cloned, amplified DNA segment from the HSR of one of the neuroblastoma lines is amplified in a subset of the lines in which NB-19-21 is amplified. In addition, this probe identifies a novel joint in the amplification unit of one line relative to that of the others. We suggest that, in the eight lines which have amplified NB-19-21, the amplification units are overlapping, but not identical, and that transposition of the common sequences may occur prior to amplification.

330. L-MYC, A NEW MYC-RELATED GENE AMPLIFIED AND EXPRESSED IN HUMAN SMALL CELL LUNG CANCER

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Nature: 318(6041):69-73 1985

Altered structure and regulation of the c-myc proto-oncogene have been associated with a variety of human tumours and derivative cell lines, including Burkitt's lymphoma, promyelocytic leukaemia and small cell lung cancer (SCLC). The N-myc gene, first detected by its homology to the second exon of the c-myc gene, is amplified and/or expressed in tumours or cell lines derived from neuroblastoma, retinoblastoma and SCLC. Here we describe a third myc-related gene (L-myc) cloned from SCLC DNA with homology to a small region of both the c-myc and N-myc genes. Human genomic DNA shows an EcoRI restriction fragment length polymorphism (RFLP) of L-myc defined by two alleles (10.0- and 6.6-kilobase (kb) EcoRI fragments), neither associated disproportionately with SCLC. Mouse and hamster DNAs exhibit a 12-kb EcoRI L-myc homologue, which indicates conservation of the gene in mammals. Gene mapping studies assign L-myc to human chromosome region 1p32, a location distinct from that of either c-myc or N-myc but associated with cytogenetic abnormalities in certain human tumours. This L-myc sequence is amplified 10-20-fold in four SCLC cell line DNAs and in one SCLC tumour specimen taken directly from a patient. Either the 10.0- or 6.6-kb allele can be amplified and in heterozygotes only one of the two alleles was amplified in any SCLC genome. SCLC cell lines with amplified L-myc sequences express L-myc-derived transcripts not seen in SCLC with amplified c-myc or N-myc genes. In addition, some

SCLCs without amplification also express L-myc-related transcripts. Together, these findings suggest an enlarging role for myc-related genes in human lung cancer and provide evidence for the concept of a myc family of proto-oncogenes.

B.

AMPLIFICATION OF RAS ONCOGENES

331. A HUMAN GASTRIC CARCINOMA CONTAINS A SINGLE MUTATED AND AN AMPLIFIED NORMAL ALLELE OF THE KI-RAS ONCOGENE

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Nucleic Acids Res, 14(3):1209-17 1986

The DNA from various human tumors and tumor cell lines was screened for the presence of mutated ras oncogenes with synthetic oligonucleotide probes, as well as with the NIH/3T3 cell transfection assay. Among the various mutations found we discovered two novel Ki-ras mutations in codon 12: gly to ala and gly to ser. A gastric carcinoma was found to possess a single mutated Ki-ras allele (gly-12 to ser), as well as a 30-50 fold amplified normal allele. This implies that two activating steps must have occurred in this malignancy.

332. C-KI-RAS AMPLIFICATION IN HUMAN LUNG CANCER

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Br J Cancer, 53(2):285-7 1986

Keywords (MeSH): Adenocarcinoma/familial and genetic; Carcinoma, Oat Cell/familial and genetic; Carcinoma, Squamous Cell/familial and genetic; Deoxyribonucleotides/analysis; DNA, Neoplasm; *Gene Amplification; Human; Lung Neoplasms/*familial and genetic; *Oncogenes.

333. A METHOD TO DETECT AND CHARACTERIZE POINT MUTATIONS IN TRANSCRIBED GENES: AMPLIFICATION AND OVEREXPRESSION OF THE MUTANT C-KI-RAS ALLELE IN HUMAN TUMOR CELLS

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Proc Natl Acad Sci USA, 82(22):7575-9 1985

A significant percentage of human tumors contain activated ras oncogenes that have acquired oncogenic potential as a result of somatic point mutations at codon 12 or 61 of the encoded ras gene product. We report here a method to detect and characterize mutations in ras genes that is based on the ability of pancreatic ribonuclease (RNase A; EC 3.1.27.5) to cleave RNA heteroduplexes containing single-base mismatches. Using this method, we show that certain human tumor cells contain mutant c-Ki-ras genes, and we define the nature and position of these mutations. At the same time, we describe the presence and estimate the expression of both normal and mutant c-Ki-ras alleles in the same tumor cells. This method should be useful for the diagnostic detection and characterization of single point mutations in expressed genes.

334. AMPLIFICATION OF ACTIVATED C-HA-RAS-1 IN HUMAN MELANOMA

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Jpn J Cancer Res; 76(7):555-8 1985

Two alleles of c-Ha-ras-1 in a human melanoma could be distinguished by restriction fragment length polymorphism, and one of them was demonstrated to be amplified 10-20 times by hybridization to a specific probe. Molecular cloning and nucleotide sequence analysis revealed that the amplified allele contained the activated c-Ha-ras-1. In the ras family, amplification of c-Ki-ras-2 and c-Ha-ras-1 has been demonstrated in several human tumors. However, the present result provides the first direct evidence that gene amplification occurs in the activated allele.

335. STABILITY OF C-K-RAS AMPLIFICATION DURING PROGRESSION IN A PATIENT WITH ADENOCARCINOMA OF THE OVARY

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Cancer Res; 45(9):4468-72 1985

We have identified a case of serous cystadenocarcinoma of the ovary in which the tumor cells display an amplification (from 10- to 20-fold) of the cellular oncogene K-ras. Normal cells purified from the malignant ascites did not show such amplification. Five consecutive samples were obtained by paracentesis over a 9-month period during which the patient received chemotherapy and underwent clinical progression. The level of c-K-ras amplification in the tumor cells did not change during this period. In studies of the tumors of 6 additional patients with adenocarcinoma of the ovary and 5 cell lines of the same histology, we have detected no other example of significant c-K-ras amplification.

336. AMPLIFICATION AND ENHANCED EXPRESSION OF CELLULAR ONCOGENE C-KI-RAS-2 IN A HUMAN EPIDERMAL CARCINOMA OF THE LUNG

Miyaki M, Sato C, Matsui T, Koike M, Mori T, Kosaki G, Takai S, Tonomura A, Tsubida N
Tokyo Metropolitan Institute of Medical Science.
Cancer; 76(4):260-5 1985

The level of c-Ki-ras-2-specific mRNA was found to be markedly enhanced (10- to 20-fold) in a human epidermal lung carcinoma transplanted into nude mice, compared with that in other lung carcinomas. Analysis of DNA revealed that c-Ki-ras-2 gene was amplified approximately 10-fold in this carcinoma, while c-Ha-ras, c-myc and c-sis were not amplified. Chromosome abnormalities were also observed in this carcinoma.

337. STUDIES ON FOUR CELLULAR PROTO-ONCOGENES AND THEIR EXPRESSION IN PCC4 EMBRYONAL CARCINOMA CELLS: AMPLIFICATION OF C-KI-RAS ONCOGENE

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Biochem Biophys Res Commun; 128(2):513-9 1985

We examined the expression of four cellular proto-oncogenes in two teratocarcinoma cell lines, one undifferentiated and malignant (PCC4), one differentiated and non malignant (PCD1). In this paper we report that transcript levels of c-Ki-ras, c-myc and c-fos are significantly higher in PCC4 cells whereas transcripts of c-Ha-ras are unchanged. Southern blot analysis does not reveal any structural alteration of c-myc and c-fos in PCC4 cells. On the contrary, the c-Ki-ras proto-oncogene is amplified 10 to 20 fold in PCC4 cells.

338. VARYING DEGREES OF AMPLIFICATION OF THE N-RAS ONCOGENE IN THE HUMAN BREAST CANCER CELL LINE MCF-7

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Cancer Res; 45(5):2201-5 1985

The oncogene N-ras has been found to be amplified (congruent to 20 copies) in the human breast carcinoma cell line MCF-7. The amplified sequences have been localized to a marker chromosome by in situ hybridization. Sublines of MCF-7, serially passaged in different laboratories, have marked variation in the degree of N-ras amplification. The differing degrees of amplification of N-ras are further evidence of heterogeneity within MCF-7 subclones. The phenomenon may not have general relevance for breast cancer, since other breast cancer cell lines and DNA from patient biopsies failed to show evidence of N-ras amplification.

339. ACTIVATION OF THE C-K-RAS ONCOGENE IN A HUMAN PANCREAS CARCINOMA

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Biochem Biophys Res Commun; 127(1):168-74 1985

The human pancreas carcinoma cell line T3M-4 contains activated c-Kirsten (K)-ras oncogene detectable by the DNA-mediated gene transfer technique using NIH/3T3 cells. DNA fragments containing coding lesions have been cloned, and nucleotide sequence analysis suggests that the T3M-4 oncogene has been activated by a single nucleotide transition from A to C in the second exon, which results in the substitution of histidine for glutamine in codon 61 of the predicted amino acid sequence. The quantity analysis of c-K-ras oncogene in the DNA and RNA of T3M-4 cells revealed that the c-K-ras gene was amplified and overexpressed in T3M-4 cells. These findings indicate that the T3M-4 c-K-ras oncogene is activated by different mutational events.

340. FREQUENCY OF MOLECULAR ALTERATIONS AFFECTING RAS PROTOONCOGENES IN HUMAN URINARY TRACT TUMORS

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Proc Natl Acad Sci USA; 82(11):3849-53 1985

Members of the ras gene family are activated as oncogenes in many different human cancers. To systematically determine the frequency at which such genes might be involved in the neoplastic process affecting a specific target tissue, urothelial cells, we surveyed a large series of urinary tract tumors for ras oncogenes by DNA transfection and by molecular genetic analysis. Harvey (Ha)-ras oncogenes were detected in 2 of 38 tumors by transfection, molecularly cloned in biologically active form, and shown to contain single base changes at codon 61 leading to substitutions of arginine and leucine, respectively, for glutamine at this position. One additional Ha-ras oncogene was identified in a bladder carcinoma by restriction polymorphisms at codon 12. In one of 21 tumors, we observed a 40-fold amplification of the Kirsten (Ki)-ras gene. No amplification of other ras genes was detected in any of the tumors analyzed. Our findings strengthen the conclusion that codons 12 and 61 are the major 'hot spots' of ras oncogene activation and suggest that quantitative alterations in expression due to gene amplification may provide an alternative mechanism for ras gene activation in primary human tumors.

341. C-HA-RAS-1 PROTO-ONCOGENE AMPLIFICATION AND OVEREXPRESSION DURING THE LIMITED REPLICATIVE LIFE SPAN OF NORMAL HUMAN FIBROBLASTS

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J Biol Chem; 260(10):6404-9 1985

The cellular proto-oncogene c-Ha-ras-1 undergoes up to 4-fold amplification during the limited replicative life span of normal human diploid fibroblasts in vitro. Levels of c-Ha-ras-1 messenger RNA and its p21 protein product are correspondingly elevated. Cellular proto-oncogene amplification and overexpression, although frequently associated with tumorigenesis, may thus occur during normal cellular growth.

342. AMPLIFICATION OF C-KI-RAS GENE AND ABERRANT EXPRESSION OF C-MYC IN WI-38 CELLS TRANSFORMED IN VITRO BY GAMMA-IRRADIATION

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Department of Biochemistry, Toyama Medical and Pharmaceutical University School of Medicine, Japan.
Biochem Biophys Res Commun; 128(2):1037-43 1985

The expression of c-oncogenes was examined with normal human fibroblasts (WI-38) and the cells transformed in vitro by gamma-irradiation (CT-1). The amount of Ki-ras-specific mRNA in CT-1 cells was found to be approximately twice that in WI-38 cells. By Southern blot hybridization, the c-Ki-ras 2 gene of CT-1 cells was found to be amplified about two-fold. CT-1 cells have higher levels of c-myc mRNA than normal cells, although the gene dosage and the restriction nuclease pattern of the c-myc gene was the same. The content of c-myc mRNA in CT-1 cells was found to be constitutively high, whereas that in normal cells was increased by serum addition.

343. [NOVEL TRANSFORMING GENES DETECTED IN HUMAN STOMACH CANCER CELLS]

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Gan To Kagaku Ryobo; 12(3 Pt 2):641-5 1985

The DNAs of six human stomach cancer cell lines were analysed, and specific gene amplification was observed; namely, an 8-fold amplified c-Ki-ras-2 gene (1 case) and a 20-fold amplified c-myc gene (1 case). In addition, it was found that a single 11-kbp-Eco-R1 fragment, having weak homology to the Ki-ras gene, was amplified 5-10 fold in three out of the six cell lines. The DNAs of two of these three cell lines gave rise to foci upon transfection into NIH3T3 cells and the primary and secondary transformants seemed to carry a similar 11-kbp-Eco-R1 fragment. It was also found that one of the DNAs from human stomach cancers gave rise to NIH3T3 cell foci upon DNA transfection. DNAs of secondary transformants commonly retained six Eco-R1 fragments that contained human Alu repeats. The size of this gene was estimated to be about 50 kbp. The Southern blot hybridization profile of this gene revealed it to be clearly different from known active human oncogenes. Furthermore, about 70% of this gene has been isolated and portions of it used as probes to test for homologies to known viral oncogenes. The gene appears to be unrelated to 14 viral oncogenes so far tested.

344. AMPLIFIED EXPRESSION OF P21 RAS PROTEIN IN HORMONE-DEPENDENT MAMMARY CARCINOMAS OF HUMANS AND RODENTS

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Biochem Biophys Res Commun; 127(2):699-706 1985

Western blotting analysis was utilized to determine the amount of a ras oncogene product, p21 present in mammary carcinomas of humans and rats. The levels of p21 in hormone-dependent rat tumors was about 7-fold that of hormone-independent tumors. The majority of human breast carcinomas examined had high p21 levels, about 10-fold that of the normal breast tissue; 70% of these tumors were estrogen and progesterone receptor positive. p21 levels in the remaining tumors were 3-fold that of the normal breast tissue, regardless of the receptor status. Fibroadenomas and fibrocystic disease showed p21 levels similar to that of the normal mammary glands. Moreover, the high p21 levels in the mammary carcinomas correlated directly with high GTPase activity, as revealed by the photo-incorporation of 8-N3-[gamma-32P]GTP into the tumor lysates. The results suggest that hormone-dependency of mammary carcinomas may correlate with quantitative change in 'normal' p21 protein.

345. STRUCTURE AND EXPRESSION OF AMPLIFIED CKI-RAS GENE SEQUENCES IN Y1 MOUSE ADRENAL TUMOR CELLS

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EMBO J; 4(5):1199-203 1985

A recombinant library of double minute chromosomal DNA, enriched in specific sequences that are amplified in Y1 mouse adrenal tumor cells, was used as a source of material to explore the structure and expression of amplified cKi-ras genes in these cells. From DNA sequence analysis of these cloned fragments, we found no evidence for the presence of point mutations previously demonstrated to be associated with activation of the transforming potential of ras genes. A comparison of the mouse gene with that of the homologous human cKi-ras2 gene reveals 94% nucleotide sequence homology within the coding regions and 97% homology for the predicted amino acid composition. Like the human gene, the mouse cKi-ras gene contains alternative 3' coding exons. Blot hybridization analyses of RNA revealed a preferential utilization of the more 3' of the two fourth coding exons in the generation of Y1 cKi-ras transcripts.

346. AMPLIFIED DNA IN Y1 MOUSE ADRENAL TUMOR CELLS: ISOLATION OF CDNAS COMPLEMENTARY TO AN AMPLIFIED C-KI-RAS GENE AND LOCALIZATION OF HOMOLOGOUS SEQUENCES TO MOUSE CHROMOSOME 6

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Nucleic Acids Res; 12(6):2731-43 1984

We have isolated cDNA clones complementary to a c-Ki-ras cellular oncogene that is amplified in Y1 mouse adrenal tumor cells, with the amplified sequences located on double-minute chromatin bodies (DMs) and homogeneously staining chromosomal regions (HSRs). Characterization of the cDNAs included the isolation of corresponding genomic clones, Northern blot analysis of RNA, and DNA sequence analysis. Our studies demonstrate that the c-Ki-ras gene amplified in the Y1 cells is homologous to the human c-Ki-ras2 gene. We have also obtained evidence that, in addition to c-

Ki-ras, at least one other transcription unit has been amplified in the mouse adrenal tumor cells. Moreover, by Southern blot analysis of Chinese hamster-mouse somatic cell hybrids, we have determined that the amplified DNA sequences associated with DMs and HSRs, including the c-Ki-ras gene, are present in normal mouse cells on chromosome 6.

347. TUMORIGENICITY OF HUMAN HT1080 FIBROSARCOMA X NORMAL FIBROBLAST HYBRIDS: CHROMOSOME DOSAGE DEPENDENCY

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Cancer Res; 44(8):3471-9 1984

The tumorigenic capacity of hybrids formed by fusion of the highly tumorigenic HT1080 human fibrosarcoma cell line with nontumorigenic normal fibroblasts was examined. The HT1080 also contains an activated N-ras oncogene. Near-tetraploid hybrids which contained an approximately complete chromosomal complement from both parental cells were nontumorigenic when 1×10^7 cells were injected s.c. into athymic (nude) mice, whereas the parental HT1080 cells produced tumors in 100% of the animals with no latency period following injection of 2×10^6 cells. Tumorigenic variants were obtained from these hybrids which had lost only a few chromosomes compared to cells from the nontumorigenic mass cultures. In addition, several near-hexaploid hybrids were obtained which contained approximately a double chromosomal complement from the HT1080 parental line and a single chromosomal complement from the normal fibroblasts. All of these near-hexaploid hybrids produce tumors in 100% of nude mice with no latency period. Our results indicate that tumorigenicity of these particular human malignant cells of mesenchymal origin can be suppressed when fused with normal diploid fibroblasts. In addition, the results suggest that tumorigenicity in this system is chromosomal dosage dependent, since a diploid chromosomal complement from normal fibroblasts is capable of suppressing the tumorigenicity of a near-diploid but not a near-tetraploid chromosomal complement from the tumorigenic HT1080 parent. Finally, the loss of chromosome 1 (the chromosome to which the N-ras oncogene has been assigned) as well as chromosome 4 was correlated with the reappearance of tumorigenicity in the rare variant populations from otherwise nontumorigenic near-tetraploid hybrid cultures. Our results also suggest the possibility that tumorigenicity in these hybrids may be a gene dosage effect involving the number of activated N-ras genes in the hybrids compared to the gene(s) controlling the suppression of the activated N-ras genes.

348. EXPRESSION OF C-RAS AND C-MYC ONCOGENES IN MURINE ERYTHROLEUKEMIAS INDUCED BY FRIEND VIRUSES

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Leuk Res; 8(6):975-84 1984

We have examined the expression of three cellular oncogenes (c-Ki-ras, c-Ha-ras and c-myc) in different stages of murine erythroleukemias induced in ICFW mice by Friend viruses (F-MuLV and SFFV) in comparison to normal mice spleens and bone marrows, including erythropoietically-stimulated spleens from phenylhydrazine-treated mice. There is no evidence of c-Ki-ras RNA expression in any of the tissues tested. c-Ha-ras RNA was found at similar levels in erythroleukemic cells and normal erythroid cells. In contrast, increased levels of normal 2.3 Kb and short 1.8 Kb c-myc

RNA transcripts were detected in both early preleukemic and late leukemic phases of the diseases, as compared to normal erythroid cells. Apparently, neither myc gene amplification nor myc gene rearrangement was observed in erythroleukemias. Our results suggest a possible involvement of c-myc gene either in erythroid cell differentiation or in an early proliferation step of the erythroleukemic process.

349. PRESENCE OF PAPILLOMAVIRUS GENOMES AND AMPLIFICATION OF THE C-MYC AND C-HA-RAS ONCOGENES IN INVASIVE CANCERS OF THE UTERINE CERVIX

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C R Seances Acad Sci IJIN; 299(14):575-80 1984

Invasive squamous cell carcinomas of the uterine cervix from 12 untreated patients were examined for the presence of human papillomavirus (HPV) genomes and for the state of the oncogenes c-myc and c-Ha-ras. Blot hybridization experiments have demonstrated the presence of the genome of HPV type 16 (HPV 16) in six tumors and that of the genomes of HPV types weakly related to HPV 16 or HPV 18 in five others. In the nine tumors corresponding to advanced stages of the disease (stages 3 and 4) there was a 3-30 fold amplification of c-myc and/or c-Ha-ras. A concomitant amplification of both oncogenes was found in eight cancers. In only one of the three tumors confined to the cervix (stage 1), the oncogene c-Ha-ras was weakly amplified. Neither HPV DNA sequences, nor oncogene amplification were detected in the leukocytes of five patients. Thus, it seems likely that specific HPV types play a role in the development of carcinomas of the uterine cervix, and that cellular oncogenes, activated through an amplification process, are involved in at least some steps of tumor progression.

350. A NOVEL COMBINATION OF K-RAS AND MYC AMPLIFICATION ACCOMPANIED BY POINT MUTATIONAL ACTIVATION OF K-RAS IN A HUMAN LUNG CANCER

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EMBO J; 3(12):2943-6 1984

Amplifications of two oncogenes, c-K-ras-2 and c-myc, were found in a human lung giant cell carcinoma (LGCC) Lu-65, which is maintained in nude mice. The extent of c-K-ras-2 and myc amplifications were estimated to be 10- and 8-fold, respectively, by means of the Southern hybridization procedure. In addition, NIH3T3 cells were transformed by transfection of Lu-65 DNA and the transforming gene was identified as c-K-ras-2. c-K-ras-2 genes were cloned from a gene library of Lu-65 and a single point mutation causing a substitution of cysteine for glycine in codon 12 was found by DNA sequencing. It was concluded that the amplification of the c-myc and c-K-ras-2 genes are accompanied by point mutational activation of c-K-ras-2 in the human LGCC Lu-65. This is the first report of multiple gene amplification accompanied by a point mutation of oncogenes in human cancer cells, providing further support for the idea that co-operation of at least two activated cellular oncogenes is required for carcinogenesis.

351. IN VIVO AMPLIFICATION AND REARRANGEMENT OF THE C-HA-RAS-1 SEQUENCE IN A HUMAN BLADDER CARCINOMA

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Biochemistry Division, National Cancer Center Research Institute, Tokyo.

Cancer; 74(6):798-801 1983

Southern blot analyses revealed amplification and rearrangement of c-Ha-ras-1 sequence in the DNA of one biopsied specimen of bladder carcinoma. DNA from normal cells, leukocytes, of the same patient showed no such changes. Therefore, the amplification and rearrangement described here seem to be associated with the development of the cancer.

352. A CELLULAR ONCOGENE (C-KI-RAS) IS AMPLIFIED, OVEREXPRESSED, AND LOCATED WITHIN KARYOTYPIC ABNORMALITIES IN MOUSE ADRENOCORTICAL TUMOUR CELLS

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Department of Microbiology and Immunology, University of California Medical Center, San Francisco, California.

Nature; 303(5917):497-501 1983

The cellular oncogene c-Ki-ras is amplified 30- to 60-fold in cells of the mouse adrenocortical tumour Y1. The amplified oncogene is located in double minute chromosomes and in a homogeneously staining chromosomal region, common karyotypic anomalies of tumour cells. The amounts of c-Ki-ras specific mRNA and of the protein (p21) encoded by the amplified gene are correspondingly elevated. Amplification and enhanced expression of cellular oncogenes may contribute to the genesis and/or maintenance of at least some naturally occurring tumours.

353. CHARACTERIZATION OF A HUMAN COLON/LUNG CARCINOMA ONCOGENE

McCoy MS, Toole JJ, Cunningham JM, Chang EH, Lowy DR, Weinberg RA

Center for Cancer Research, Department of Biology, Massachusetts Institute of Technology, Cambridge.

Nature; 302(5903):79-81 1983

DNA sequences capable of inducing oncogenic transformation of NIH3T3 mouse cells are found in a number of human tumour cell lines. When DNAs of these cell lines are applied to monolayer cultures of the mouse fibroblasts, foci of transformed cells are observed 2-3 weeks later. DNA from cells of such primary foci can be used in turn to induce foci in a second cycle of gene transfer. The human DNA sequences responsible for transformation have been called oncogenes, the best characterized of which is closely related to the Harvey murine sarcoma virus oncogene. Here we present a characterization of an oncogene which we found originally to be present in DNA of the SW480 colon carcinoma cell line. We indicate its structural outlines and demonstrate, in extension of reported results, its presence in an activated form in the genome of several types of human tumour cell lines as well as in biopsy tissue from an adenocarcinoma of the large bowel. We identify this tumour oncogene with c-Ki-ras2, one of two known members of the Kirsten ras family of human proto-oncogenes, extending a series of recent reports which have demonstrated homologies between human oncogenes and those of Harvey and Kirsten murine sarcoma viruses. The c-Ki-ras2 oncogene of several tumour cell lines is shown to be amplified.

354. AMPLIFICATION AND REARRANGEMENT OF ONC GENES IN MAMMALIAN SPECIES

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Nature; 296(5855):361-363 1982

Amplification and rearrangement of transforming (onc) genes was investigated in mammalian species. Sequences related to each onc have been identified in all vertebrate species tested, usually one per haploid genome. The rat has at least two different genes homologous to the onc of the rat-derived Harvey murine sarcoma virus (Ha-MuSV). Evidence for the relatively recent amplification of the genes was found by screening genomic DNA from several rodent sequences related to the onc of Ha-MuSV and to the closely related onc of Kirsten (Ki) MuSV. The ras sequences in rodent DNA were studied by electrophoresis and hybridization to a probe derived either from the v-Ha-ras (the onc gene of Ha-MuSV) or v-Ki-ras (the onc gene of Kirsten MuSV). The pattern of c-ras fragments was distinctive for the DNAs from mink, rat, and other Mus species, while the v-Ha-ras probe detected the same c-ras fragments in all M musculus, M castaneus and M poschiavinus. In contrast to the relatively few c-ras fragments in other species, the DNA of a M pahari cell line contained many fragments, representing at least 10 copies per haploid genome. Amplification in M pahari apparently consists of c-Ha-ras sequences; such an occurrence does not seem to be the result of in vitro propagation of the cell line. Genomic DNA from Chinese hamster ovary cells digested with EcoRI contained at least eight fragments which hybridized to the v-Ki-ras probe, while Syrian hamster DNA contained only one such fragment. Possible mechanisms leading to amplification of the ras genes are discussed. (30 Refs)

C.

AMPLIFICATION OF OTHER ONCOGENES

355. EXPRESSION OF THE C-MYB ONCOGENE IN HUMAN SMALL CELL LUNG CARCINOMA

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Cancer Res; 45(1):272-5 1985

We have found that the oncogene c-myb is differentially expressed in human lung cancer cell lines and that myb-homologous RNA can be detected only in small cell lung cancer (SCLC) cell lines. Polyadenylic acid-RNA from 13 established cell lines was examined by Northern blotting for its ability to hybridize to a radiolabeled v-myb probe. A 3.5-kilobase RNA transcript homologous to v-myb is present in four of four lines of classic SCLC and in three of four SCLC variant lines but not in five of five non-small cell lung cancer lines tested. This transcript is the same size as that found in the immature myeloid cell lines KG1, but the amount of RNA is only about 10% of that in the KG1 line. A second transcript hybridizing to v-myb, 2.4 kilobases in size, is also present in the variant SCLC lines and the COLO 320 line, all of which have amplification of the c-myc gene and markedly increased c-myc messenger RNA. The presence of myb transcripts in SCLC suggests that the myb gene may have a specific role in the initiation or maintenance of an important human epithelial tumor.

356. AMPLIFICATION OF THE C-MYB ONCOGENE IN A CASE OF HUMAN ACUTE MYELOGENOUS LEUKEMIA

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Science; 224(4653):1117-21 1984

Amplification is one of the mechanisms by which cellular oncogenes may be altered in their function, possibly leading to neoplastic transformation. The oncogenes c-myc, c-abl, and c-Ki-ras are amplified in several different human neoplasias. The oncogene c-myb, which is specifically expressed and regulated in hematopoietic cells, was found to be amplified in cell lines ML-1, ML-2, and ML-3, which were separately cultured from cells of a patient with acute myelogenous leukemia (AML). A five- to tenfold amplification was correlated with high levels of expression of normal size c-myb messenger RNAs and with chromosomal abnormalities in the region 6q22-24, where the c-myb locus is normally located. Amplification and cytogenetic abnormalities were detected in DNA's from primary and secondary cultures of ML cells, suggesting that they may have contributed to leukemogenesis. The similar AML cell lines HL-60 and ML-3 contain different amplified oncogenes: c-myc and c-myb, respectively. Alternative activation of structurally and possibly functionally similar oncogenes may distinguish - at the pathogenetic level - phenotypically similar tumors.

357. MAPPING OF AMPLIFIED C-MYB ONCOGENE, SISTER CHROMATID EXCHANGES, AND KARYOTYPIC ANALYSIS OF THE COLO 205 COLON CARCINOMA CELL LINE

Winqvist R, Knuutila S, Leprince D, Siebelin D, Alitalo K

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Cancer Genet Cytogenet; 18(3):251-64 1985

We have studied molecular and chromosomal details of cytogenetic status in a human tumor cell line COLO 205 that shows a stable, approximately tenfold amplification of the c-myb oncogene. The amplified copies of c-myb reside in two marker chromosomes that may have evolved from chromosome 6 by complex chromosomal rearrangements. No homogeneously staining regions can be discerned at the site of c-myb amplification. We suggest that c-myb was amplified in situ in a chromosomal segment (6q22-24) that became a part of the marker chromosome, possibly through isochromosome formation followed by duplication, and without the extrachromosomal intermediate form of double minute chromosomes. There is an enhanced frequency of sister chromatid exchanges at the site of amplified c-myb. These results are discussed in the context of models for gene amplification and oncogene activation.

358. ABERRANT EXPRESSION OF AN AMPLIFIED C-MYB ONCOGENE IN TWO CELL LINES FROM A COLON CARCINOMA

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Proc Natl Acad Sci USA; 81(14):4334-8 1984

Two cell lines (COLO 201 and COLO 205) derived independently from a single adenocarcinoma of the human colon each harbored an approximately 10-fold amplification of the cellular oncogene c-myb and a proportional abundance of the 4-kilobase mRNA derived from c-myb. By contrast, expression of c-myb could not be detected in cells from a variety of other solid tumors, including other colon carcinomas. Analysis of the amplified DNA with restriction endonu-

cleases failed to reveal any topographical abnormalities within c-myb. Neither COLO 201 nor COLO 205 carry the double minute chromosomes and homogeneously staining regions of chromosomes that frequently serve as karyotypic signatures of amplified DNA. Instead, amplified c-myb is carried on what appear to be disomic or trisomic copies of the same anomalous marker chromosome that is characteristic of both COLO 201 and COLO 205. The karyological origin of this abnormal chromosome is not presently apparent. Our findings show c-myb expression by cells outside of the hematopoietic lineage, raise the possibility that amplification and/or ectopic expression of c-myb may have contributed to the genesis of the tumor from which the cells of COLO 201 and COLO 205 arose, and suggest that amplification of cellular oncogenes may be a more common factor in tumorigenesis than might have been suspected from available karyological data.

359. AMPLIFICATION OF C-ERBB-2 ONCOGENE IN HUMAN ADENOCARCINOMAS IN VIVO

Yokota J, Yamamoto T, Toyoshima K, Terada M, Sugimura T, Battifora H, Cline MJ

University of California at Los Angeles

Lancet; 1(8484):765-7 1986

There are two genes related to the viral erbB gene in the human genome. c-erbB-1 is the same as the gene for the epithelial-growth-factor (EGF) receptor, and c-erbB-2 encodes a receptor-like protein very similar to, but distinct from, the EGF receptor. Hybridisation analysis of DNA from 101 fresh human malignant tumours showed that the c-erbB-2 gene was amplified in 5 of 63 adenocarcinomas and none of 38 other types of tumours, whereas the c-erbB-1/EGF-receptor gene was amplified only in 1 of 8 squamous-cell carcinomas. Thus, the protein products of the amplified c-erbB-2 gene may have a role in the evolution of adenocarcinomas, as does the EGF receptor in some squamous-cell carcinomas.

360. SIMILARITY OF PROTEIN ENCODED BY THE HUMAN C-ERB-B-2 GENE TO EPIDERMAL GROWTH FACTOR RECEPTOR

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Nature; 319(6050):230-4 1986

A novel v-erbB-related gene, c-erbB-2, which has been identified in the human genome, maps to human chromosome 17 at q21 (ref. 40), and seems to encode a polypeptide with a kinase domain that is highly homologous with, but distinct from, that of the epidermal growth factor (EGF) receptor. The c-erbB-2 gene is conserved in vertebrates and it has been suggested that the neu gene, detected in a series of rat neuro/glioblastomas, is, in fact, the rat c-erbB-2 gene. Amplification of the c-erbB-2 gene in a salivary adenocarcinoma and a gastric cancer cell line MKN-7 suggests that its over-expression is sometimes involved in the neoplastic process. To determine the nature of the c-erbB-2 protein, we have now molecularly cloned complementary DNA for c-erbB-2 messenger RNA prepared from MKN-7 cells. Its sequence shows that the c-erbB-2 gene encodes a possible receptor protein and allows an analysis of the similarity of the protein to the EGF receptor and the neu product. As a consequence of chromosomal aberration in MKN-7 cells, a 4.6-kilobase (kb) normal transcript and a truncated 2.3-kb transcript of c-erbB-2 are synthesized at elevated levels. The latter transcript presumably encodes only the extracellular domain of the putative receptor.

361. AMPLIFICATION OF A NOVEL V-ERBB-RELATED GENE IN A HUMAN MAMMARY CARCINOMA

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Science; 229(4717):974-6 1985

The cellular gene encoding the receptor for epidermal growth factor (EGF) has considerable homology to the oncogene of avian erythroblastosis virus. In a human mammary carcinoma, a DNA sequence was identified that is related to v-erbB but amplified in a manner that appeared to distinguish it from the gene for the EGF receptor. Molecular cloning of this DNA segment and nucleotide sequence analysis revealed the presence of two putative exons in a DNA segment whose predicted amino acid sequence was closely related to, but different from, the corresponding sequence of the erbB/EGF receptor. Moreover, this DNA segment identified a 5-kilobase transcript distinct from the transcripts of the EGF receptor gene. Thus, a new member of the tyrosine kinase proto-oncogene family has been identified on the basis of its amplification in a human mammary carcinoma.

362. [A MEMBER OF THE SRC GENE FAMILY, THE C-ERBB-1 GENE, IS CLOSELY RELATED TO THE EGF RECEPTOR GENE]

Yamamoto T, Kawai S, Toyoshima K
Institute of Medical Science, Tokyo University.
Gan To Kagaku Ryobo; 12(3 Pt 2):632-40 1985

An avian erythroblastosis virus, AEV-H, induces both erythroblastosis and sarcomas in susceptible chickens. Since AEV-H carries the v-erbB as a sole oncogene, the erbB gene was suggested to be responsible for the induction of these tumors. Analysis of the amino acid sequence predicted from the nucleotide sequence of the v-erbB gene revealed that the gene product has a domain characteristic for tyrosine kinase. Recently in has been suggested the v-erbB protein is a part of the chicken EGF (epidermal growth factor) receptor. Using antibody against either v-erbB protein or EGF receptor, we also demonstrated close similarity between the two proteins. Further studies on human genomic DNA revealed that the c-erbB-1 gene, a proto-oncogene of the v-erbB gene, is the EGF receptor gene. We were also able to identify the c-erbB-2 gene that seems to code for a EGF receptor-like protein with a domain for tyrosine kinase. Finally, we would like to show that cell lines established from human squamous cell carcinoma are frequently associated with amplification of the c-erbB-1/EGF receptor gene.

363. A V-ERBB-RELATED PROTOONCOGENE, C-ERBB-2, IS DISTINCT FROM THE C-ERBB-1/EPIDERMAL GROWTH FACTOR-RECEPTOR GENE AND IS AMPLIFIED IN A HUMAN SALIVARY GLAND ADENOCARCINOMA

Semba K, Kamata N, Toyoshima K, Yamamoto T
Institute of Medical Science, University of Tokyo, Japan.
Proc Natl Acad Sci USA; 82(19):6497-501 1985

From a human genomic library, we obtained six v-erbB-related DNA clones. A DNA probe prepared from one of the clones, lambda 107, hybridized to EcoRI fragments of 6.4 and 13 kilobase pairs of human DNA. Neither of these fragments was amplified in A431 vulva carcinoma cells, in which the gene encoding the epidermal growth factor receptor is amplified. In addition, the probe from lambda 107 hybridized with a single, 4.8-kilobase poly(A)⁺ RNA species and did not react with EGF receptor mRNA. Thus, we conclude that clone lambda 107 represents a v-erbB-related gene (c-erbB-2) that is distinct from the EGF receptor gene. In contrast, the other five clones were shown to represent the EGF receptor gene (c-erbB-1). Partial nucleotide sequence analysis of the

lambda 107 insert showed that this clone contained at least seven putative exons and that six of them could encode the kinase domain characteristic of protein products of the src oncogene family. Southern blot analysis showed close similarity of the restriction patterns of the rat c-erbB-2 gene and the rat *leu* oncogene, suggesting possible involvement of c-erbB-2 in human cancer. In fact, approximately 30-fold amplification of c-erbB-2 was observed in a human adenocarcinoma of the salivary gland.

364. AMPLIFIED, OVEREXPRESSED AND REARRANGED EPIDERMAL GROWTH FACTOR RECEPTOR GENE IN A HUMAN ASTROCYTOMA CELL LINE

Films J, Pollak MN, Cairncross JG, Buick RN
Ontario Cancer Institute, Toronto, Canada.
Biochem Biophys Res Commun; 131(1):207-15 1985

We report here that SK-MG-3, a human astrocytoma cell line with a high number of epidermal growth factor (EGF) receptors, has an amplified and overexpressed EGF receptor gene. Northern blot analysis did not show any abnormal EGF receptor gene-related mRNA species. No amplification or rearrangement was noted in 21 other astrocytoma cell lines. In contrast to other cell lines that have EGF receptor gene amplifications, we have not detected inhibition of in vitro proliferation of the SK-MG-3 line by EGF.

365. MDA-468, A HUMAN BREAST CANCER CELL LINE WITH A HIGH NUMBER OF EPIDERMAL GROWTH FACTOR (EGF) RECEPTORS, HAS AN AMPLIFIED EGF RECEPTOR GENE AND IS GROWTH INHIBITED BY EGF

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Ontario Cancer Institute, University of Toronto, Canada.
Biochem Biophys Res Commun; 120(2):898-905 1985

Epidermal growth factor (EGF) has been noted to stimulate proliferation of a variety of normal and malignant cells including those of human breast epithelium. We report here that MDA-468, a human breast cancer cell line with a very high number of EGF receptors, is growth-inhibited at EGF concentrations that stimulate most other cells. The basis for the elevated receptor level is EGF receptor gene amplification and over-expression. An MDA-468 clone selected for resistance to EGF-induced growth inhibition shows a number of receptors within the normal range. The results are discussed in relation to a threshold model for EGF-induced growth inhibition.

366. TRANSLOCATION CHROMOSOME 7 OF A431 CELLS CONTAINS AMPLIFICATION AND REARRANGEMENT OF EGF RECEPTOR GENE RESPONSIBLE FOR PRODUCTION OF VARIANT MRNA

Hunts JH, Shimizu N, Yamamoto T, Toyoshima K, Merlino GT, Xu YH, Pastan I
Department of Molecular and Cellular Biology, University of Arizona, Tucson 85721.
Somatic Cell Mol Genet; 11(5):477-86 1985

The epidermal growth factor (EGF) receptor, along with several oncogene protein products, possesses tyrosine-specific protein kinase activity. Furthermore, the EGF receptor has structural similarity to the putative v-erbB transforming protein. Because of these closely shared characteristics, it is important to elucidate the possible involvement of the EGF receptor in malignant transformation. The epidermal carcinoma cell line A431 exhibits an abnormally high number of EGF receptors, which is associated with the presence of translocation chromosome M4. Recently, A431 cells have been shown to contain amplified sequences for the EGF receptor gene(s) and also to produce a variant mRNA which diverges from

the normal EGF receptor mRNA at the 3' end. Here we report, using the human EGF receptor cDNA probe pE7, that the chromosome M4 has a six- to sevenfold amplification of the EGF receptor gene. Furthermore, the presence of M4 in somatic cell hybrids correlates with the production of the variant 2.9-kb mRNA. This aberrant mRNA is apparently generated by an intrachromosomal rearrangement which was detected using as a probe a fragment of the pE15cDNA encoding the variant mRNA.

367. STRUCTURE AND LOCALIZATION OF GENES ENCODING ABERRANT AND NORMAL EPIDERMAL GROWTH FACTOR RECEPTOR RNAs FROM A431 HUMAN CARCINOMA CELLS

Merlino GT, Isbii S, Whang-Peng J, Knutsen T, Xu YH, Clark AJ, Stratton RH, Wilson RK, Ma DP, Roe BA, et al
Laboratory of Molecular Biology, National Cancer Institute, Bethesda, Maryland 20205.
Mol Cell Biol. 5(7):1722-34 1985

A431 cells have an amplification of the epidermal growth factor (EGF) receptor gene, the cellular homolog of the v-erb B oncogene, and overproduce an aberrant 2.9-kilobase RNA that encodes a portion of the EGF receptor. A cDNA (pE15) for the aberrant RNA was cloned, sequenced, and used to analyze genomic DNA blots from A431 and normal cells. These data indicate that the aberrant RNA is created by a gene rearrangement within chromosome 7, resulting in a fusion of the 5' portion of the EGF receptor gene to an unidentified region of genomic DNA. The unidentified sequences are amplified to about the same degree (20- to 30-fold) as the EGF receptor sequences. In situ hybridization to chromosomes from normal cells and A431 cells show that both the EGF receptor gene and the unidentified DNA are localized to the p14-p12 region of chromosome 7. By using cDNA fragments to probe DNA blots from mouse A431 somatic cell hybrids, the rearranged receptor gene was shown to be associated with translocation chromosome M4.

368. RELATIONSHIP BETWEEN PRODUCTION OF EPIDERMAL GROWTH FACTOR RECEPTORS, GENE AMPLIFICATION, AND CHROMOSOME 7 TRANSLOCATION IN VARIANT A431 CELLS

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Department of Medicine, University of California, San Diego School of Medicine, La Jolla, California 92093.
Somatic Cell Mol Genet. 11(4):309-18 1985

Synthesis of the epidermal growth factor (EGF) receptor has been analyzed in a series of variant A431 human epidermoid carcinoma cell clones reported to contain different amounts of EGF binding sites. The amount of EGF receptor protein, quantitated by immunoaffinity chromatography, and EGF receptor mRNA, quantitated by cDNA hybridization, were closely correlated to the extent of EGF receptor gene amplification. This correlation existed in variants selected for reduced EGF receptors and in revertants from those variants with increased EGF receptors. There was also a correlation between the frequency of translocation of chromosome 7, containing the EGF receptor gene, and EGF receptor protein. These results support gene amplification as the mechanism enhancing A431 cell EGF receptor protein and determining growth responses.

369. ELEVATED EPIDERMAL GROWTH FACTOR RECEPTOR GENE COPY NUMBER AND EXPRESSION IN A SQUAMOUS CARCINOMA CELL LINE

Merlino GT, Xu YH, Richert N, Clark AJ, Isbii S, Banks-Schlagel S, Pastan I
Laboratory of Molecular Biology, National Cancer Institute, Bethesda, Maryland 20205.
J Clin Invest. 75(3):1077-9 1985

The human epidermal growth factor (EGF) receptor is known to be homologous to the v-erb B oncogene protein of the avian erythroblastosis virus. Overexpression of the EGF receptor gene in A431 epidermoid carcinoma cells is due to gene amplification. In this study, a variety of squamous cell carcinomas were examined and one, SCC-15, contained high levels of the EGF receptor as determined by immunoprecipitation via an EGF receptor-specific polyclonal antibody. Using a cloned EGF receptor complementary DNA as a probe, the level of EGF receptor RNA was found to be elevated four-fold in SCC-15 relative to normal cultured keratinocytes. When the same probe was used to identify EGF receptor gene fragments on a genomic DNA blot, the SCC-15 cell line was shown to possess an EGF receptor gene copy number amplified four to five times. Gene amplification results in the enhancement in the level of the EGF receptor in several carcinomas and could be responsible for the appearance of the transformed phenotype in these cells.

370. AMPLIFICATION, ENHANCED EXPRESSION AND POSSIBLE REARRANGEMENT OF EGF RECEPTOR GENE IN PRIMARY HUMAN BRAIN TUMOURS OF GLIAL ORIGIN

Libermann TA, Nusbaum HR, Razen N, Kris R, Lax I, Soreq H, Whittle N, Waterfield MD, Ullrich A, Schlessinger J
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Nature. 313(5998):144-7 1985

Epidermal growth factor (EGF), through interaction with specific cell surface receptors, generates a pleiotropic response that, by a poorly defined mechanism, can induce proliferation of target cells. Subversion of the EGF mitogenic signal through expression of a truncated receptor may be involved in transformation by the avian erythroblastosis virus (AEV) oncogene v-erb-B, suggesting that similar EGF receptor defects may be found in human neoplasias. Overexpression of EGF receptors has been reported for the epidermoid carcinoma cell line A431, in various primary brain tumours and in squamous carcinomas. In A431 cells the receptor gene is amplified. Here we show that 4 of 10 primary brain tumours of glial origin which express levels of EGF receptors that are higher than normal also have amplified EGF receptor genes. Amplified receptor genes were not detected in the other brain tumours examined. Further analysis of EGF receptor defects may show that such altered expression and amplification is a particular feature of certain human tumours.

371. AMPLIFICATION AND ENHANCED EXPRESSION OF THE EPIDERMAL GROWTH FACTOR RECEPTOR GENE IN A431 HUMAN CARCINOMA CELLS

Merlino GT, Xu YH, Isbii S, Clark AJ, Semba K, Toyoshima K, Yamamoto T, Pastan I
Laboratory of Molecular Biology, National Cancer Institute, Bethesda, Maryland.
Science. 224(4647):417-9 1984

The sequence of the human epidermal growth factor (EGF) receptor shows great homology with the avian erythroblastosis virus v-erb B oncogene, raising the possibility that the receptor gene is identical to the c-erb B protooncogene. Human A431 epidermoid carcinoma cells, which have an un-

usually high number of EGF receptors, were examined to determine whether elevated EGF receptor levels correlate with gene amplification. Southern blots of genomic DNA's from A431 and other human cell lines were probed with either a v-erb B gene fragment or a human EGF receptor complementary DNA clone (pE7), previously isolated from an A431 complementary DNA library. When either probe was used to analyze Eco RI- or Hind III-generated DNA fragments, EGF receptor DNA sequences were amplified about 30-fold in A431. Differences in the banding pattern of A431 DNA fragments relative to normal fibroblast DNA indicate the occurrence of a rearrangement in the region of the receptor gene. Furthermore, A431 cells contain a characteristic, prominent 2.9-kilobase RNA. These results are consistent with the hypothesis that, in A431 cells, gene amplification, possibly associated with a translocation event, may result in the overproduction of EGF receptor protein or the appearance of the transformed phenotype (or both).

372. HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR CDNA SEQUENCE AND ABERRANT EXPRESSION OF THE AMPLIFIED GENE IN A431 EPIDERMAL CARCINOMA CELLS

Ullrich A, Coussens L, Hayflick JS, Dull TJ, Gray A, Tam AW, Lee J, Yarden Y, Libermann TA, Schlessinger J, et al
Department of Molecular Biology, Genentech, Inc., South San Francisco, California.
Nature; 309(5967):418-25 1984

The complete 1,210-amino acid sequence of the human epidermal growth factor (EGF) receptor precursor, deduced from cDNA clones derived from placental and A431 carcinoma cells, reveals close similarity between the entire predicted v-erb-B mRNA oncogene product and the receptor transmembrane and cytoplasmic domains. A single transmembrane region of 23 amino acids separates the extracellular EGF binding and cytoplasmic domains. The receptor gene is amplified and apparently rearranged in A431 cells, generating a truncated 2.8-kilobase mRNA which encodes only the extracellular EGF binding domain.

373. UNSTABLE EXPRESSION AND AMPLIFICATION OF A TRANSFECTED ONCOGENE IN CONFLUENT AND SUBCONFLUENT CELLS

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98104.
Mol Cell Biol; 5(6):1456-64 1985

NIH 3T3 cells were transfected with a plasmid containing the transforming gene, v-src, from Rous sarcoma virus. One of the transformed cell lines isolated reverted to a flat, non-transformed morphology after cloning through soft agar. This cell line did not express the src gene and could no longer grow in soft agar. When these cells were held at confluence, spontaneous foci appeared which eventually covered the dish. The appearance of foci correlated with an increase in v-src gene expression, ability to grow in soft agar, and tumorigenicity in mice. When these transformed cells were trypsinized and held at subconfluence, both v-src expression and the transformed phenotype were progressively lost. Whereas rearrangement of the transfected gene was not detected, the gene copy number in the transformed cells was markedly increased (greater than 50-fold). Confluence-dependent gene amplification and deamplification have been retained after several cycles of growth alternately at high and low density, in cells recloned through soft agar, and after cells had been maintained continuously at high or low density. The results suggest that, in this cell line, reversible gene amplification plays a central role in expression of the transfected gene.

374. AMPLIFICATION AND REARRANGEMENT OF HU-ETS-1 IN LEUKEMIA AND LYMPHOMA WITH INVOLVEMENT OF 11Q23

Rovigatti U, Watson DK, Yunis JJ
Laboratory of Human Neoplasia, A. Ochsner Medical Foundation, New Orleans, LA 70121.
Science; 232(4748):398-400 1986

The Hu-ets-1 oncogene was found to be rearranged and amplified 30-fold in one case of acute myelomonocytic leukemia in which a homogeneously staining region occurred on 11q23; the oncogene was rearranged and amplified approximately tenfold in a case of small lymphocytic cell lymphoma with an inverted insertion that also involved band 11q23. This work suggests that Hu-ets-1 is an unusual oncogene that can help explain the common involvement of chromosome band 11q23 in various subtypes of hematopoietic malignancies.

375. REGIONS OF THE HUMAN GENOME CONTAINING HOMOLOGS OF THE ONCOGENES AND RETROVIRUS GENES. 3. THE PRIMARY STRUCTURE OF THE MOS-RELATED REGION CL-1 FROM THE ORAGP5 LOCUS

Zabavuskii ER, Prasolov VS, Tretyakov LO, Chumakov IM, Kiselev LI
Bioorg Khim; 11(3):380-90 1985

The nucleotide sequence of 686 bp from the cloned human genome locus gp5 has been determined. Analysis of this sequence has revealed a statistically significant homology with both the viral and murine mos genes. The region of mos homology contains two adjacent homologous domains, whereas their counterparts in viral mos gene are separated by 471 bp. The position of mos homologous region in the close vicinity to LTR of endogenous human viral-like repeat is in accordance with the hypothesis of retroviral involvement in the process of mos gene amplification.

376. AMPLIFICATION OF C-YES-1 PROTO-ONCOGENE IN A PRIMARY HUMAN GASTRIC CANCER

Seki T, Fujii G, Mori S, Tamaoki N, Shibuya M
Institute of Medical Science, University of Tokyo.
Jpn J Cancer Res; 76(10):907-10 1985

Abnormalities of cellular oncogenes in 22 cases of human primary gastric cancer were screened by Southern blot analysis using 16 onc probes. Human cellular sequences related to the v-yes oncogene of Y73 avian sarcoma virus (human c-yes-1 gene) were found to be amplified in a primary gastric cancer. The degree of amplification was about 4- to 5-fold. Another v-yes-related cellular gene (human c-yes-2, a pseudogene) was not amplified in this tumor. The normal stomach tissue adjacent to the tumor tissue in the same patient showed no amplification of c-yes-1 gene, suggesting that the amplified c-yes-1 is involved in the onset or the progress of this carcinoma.

377. VIRAL AND CELLULAR FOS PROTEINS: A COMPARATIVE ANALYSIS

Curran T, Miller AD, Zohar L, Verma IM
Molecular Biology and Virology Laboratory, Salk Institute, San Diego, California.
Cell; 36(2):259-68 1984

The FBJ murine osteosarcoma virus (FBJ-MuSV) induces osteosarcomas in mice and transforms fibroblasts in vitro. It contains an oncogene termed v-fos derived from a normal cellular gene by recombination with an associated helper virus. The product of the v-fos gene is a 55,000 dalton protein, p55v-fos. This protein was found in the nuclei of cells containing amplified levels of the v-fos gene, and also in the

nuclei of virus-transformed cells. The c-fos protein was localized in the nuclei of normal mouse amnion cells and in the nuclei of cells transformed by a recombinant plasmid that expresses the c-fos gene product. However, p55c-fos undergoes more extensive post-translational modification in the nucleus than p55v-fos. Immunofluorescence data indicate that the level of p55c-fos in normal mouse amnion cells is similar to that found in fibroblasts transformed by the v-fos or c-fos proteins.

D.

GENERAL STUDIES AND REVIEWS OF ONCOGENE AMPLIFICATION

378. GENE AMPLIFICATION IN CANCER: A MOLECULAR CYTOGENETIC APPROACH

Meltzer P, Kinzler K, Vogelstein B, Trent JM
Department of Pediatrics, University of Arizona, Tucson 84724.
Cancer Genet Cytogenet; 19(1-2):93-9 1986

Many human tumors have been shown to exhibit cytologic evidence of gene amplification. In several instances the amplified genes have proven to be cellular oncogenes. We present an approach for combining cytogenetic and molecular biological techniques to systematically investigate this phenomenon.

379. STUDIES ON THE EXPRESSION OF THE AMPLIFIED DOMAIN IN HUMAN NEUROBLASTOMA CELLS

Melera PW, Michalski RW, Montgomery KT, Bidler JL, Scotto KW, Davide JP
Laboratory of RNA Synthesis and Regulation, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
Prog Clin Biol Res; 175:115-29 1985

Keywords (MeSH): Base Sequence; Cell Line; DNA; Neoplasm/*genetics; *Gene Amplification; Human; Neuroblastoma/*familial and genetic; Oncogenes.

380. A DETAILED ANALYSIS OF CHROMOSOMAL CHANGES IN HERITABLE AND NON-HERITABLE RETINOBLASTOMA

Squire J, Gallie BL, Phillips RA
Department of Medical Biophysics, University of Toronto, Ontario, Canada.
Hum Genet; 70(4):291-301 1985

Full cytogenetic analysis of 27 different retinoblastoma tumors is presented. Gross aneuploidy of chromosome arms 6p and 1q were very common, being observed in 15/27 and 21/27 tumors, respectively. However, we found that chromosome 13 was rarely missing: only 3/27 had a detectable monosomy affecting 13q14. Monosomy of chromosome 13 by small deletion or rearrangement was also not observed in any of 12 retinoblastoma tumor lines analyzed in detail at the 300-400 chromosome band level. A novel observation in retinoblastoma was the discovery of non-random translocations at three specific breakpoints, 14q32 (4/12), 17p12 (5/12), and 10q25 (3/12). Genomic rearrangements similar to those described involving C-myc in Burkitt lymphoma 14q+ cells could not be demonstrated in the four 14q+ retinoblastoma lines using molecular techniques, and a probe mapping to the site implicated to have an activating role in lymphoma. These data suggest that there is a target for rearrangement at 14q32 but it is not the same sequence used in some Burkitt lymphomas. Two other breakpoints (2p24 and 8q24) coincided with the mapped position of cellular oncogenes, but also failed to show a molecular rearrangement with the oncogene probes. The breakpoints, 10q25 and 17p12, are constitutional fragile sites which may predispose these regions to act as acceptors of translocations in malignant cells. One line had double minute chromosomes, and was the only one of 16 (6%)

tested with the N-myc probe which had an amplification. Different tumors from single patients with multifocal heritable retinoblastoma showed independent karyotype evolution. Unilateral non-heritable tumors exhibited a high level of karyotype stability throughout both in vivo and in vitro growth. The various common patterns of aneuploidy and translocations probably confer an early selective advantage to malignant cells, rather than induce malignant transformation.

381. CYTOGENETIC AND MOLECULAR BIOLOGIC ALTERATIONS IN HUMAN BREAST CANCER: A REVIEW

Trent JM
Dept of Internal Medicine, University of Arizona College of Medicine, Tucson 85724.
Breast Cancer Res Treat; 5(3):221-9 1985

Chromosomal and molecular biologic studies of human breast cancer are beginning to provide insight into the basic biology of this important disease. The current state of knowledge of both cytogenetic evaluation and assessment of expression and amplification of cellular oncogenes in breast cancer will be outlined in this brief review. (37 Refs)

382. CHROMOSOME ABNORMALITIES, GENE AMPLIFICATION, AND TUMOR PROGRESSION (25 Refs)

Gilbert F
Dept. of Pediatrics, Mount Sinai School of Medicine, New York, New York 10029.
Prog Clin Biol Res; 175:151-9 1985

Keywords (MeSH): *Cell Transformation, Neoplastic; *Chromosome Aberrations; Chromosomes, Human, 1-3; *Gene Amplification; Human; Neuroblastoma/*familial and genetic; Oncogenes; Review.

383. HUMAN GENOME: PROTO-ONCOGENES AND PRORETROVIRUSES

Kisselev LL, Chumakov IM, Zaharovskiy ER, Prassolov VS, Mett VL, Berdichevskiy FB, Tretyakov LD
Institute of Molecular Biology, USSR Academy of Sciences, Moscow.
Folia Biol (Praga); 31(2):121-34 1985

A brief review of the studies undertaken at the Laboratory for Molecular Bases of Oncogenesis (Institute of Molecular Biology, Moscow) till middle of 1984 is presented. The human genome contains multiple dispersed nucleotide sequences related to the proto-oncogene *mos* and to proviral sequences in tight juxtaposition to each other. From sequencing appropriate cloned fragments of human DNA in phage and plasmid vectors it follows that one of these regions, NV-1, is a pseudogene of proto-*mos* with partial duplications and two Alu elements intervening its coding sequence, and the other, CL-1, seems to be also a *mos*-related gene with a deletion of the internal part of the structural gene. CL-1 is flanked by a proviral-like sequence including tRNA^{Met} binding site and U5 (part of the long terminal repeat). The proviral-like sequences are transcribed in 21-35S poly(A)+RNA abundant in normal and malignant human cells. Two hypotheses are proposed: endogenous retroviruses take part in amplification of at least some proto-oncogenes; proto-oncogenes are inactivated via insertion of movable genetic elements and conversion into pseudogenes. Potential oncogenicity of a normal human genome undergoes two controversial influences: it increases due to proto-oncogene amplification and decreases due to inactivation of some of them.

384. GENE AMPLIFICATION (246 Refs)

Stark GR, Wabl GM

Department of Biochemistry, Stanford University School of Medicine, California.

Annu Rev Biochem; 53:447-91 1984

Keywords (MeSH): Animal; Cell Differentiation; Chromosomes; Drosophila/genetics; DNA Replication; DNA/genetics; DNA, Recombinant; Extrachromosomal Inheritance; *Gene Amplification; Mammals; Models, Genetic; Neoplasms/familial and genetic; Oogenesis; Review; Tetrahymena/genetics.

385. ONCOGENES AMPLIFIED IN CANCER CELLS

Marx JL

Science; 223(4631):40-1 1984

Keywords (MeSH): Animal; Cell Line; Cell Transformation, Neoplastic; Chromosome Aberrations; *Gene Amplification; Human; Leukemia/familial and genetic; Lung Neoplasms/familial and genetic; Neoplasms/*familial and genetic/metabolism; Neuroblastoma/familial and genetic; *Oncogenes; RNA, Messenger/biosynthesis; RNA, Neoplasm/biosynthesis; Translocation (Genetics).

386. AMPLIFICATION OF CELLULAR ONCOGENES IN CANCER CELLS

Alirola K

Department of Virology, University of Helsinki, Finland.

Med Biol; 62(6):304-17 1984

Regulatory or structural alterations of cellular oncogenes have been implicated in the causation of various cancers. Oncogene alteration by point mutations can result in a protein product with strongly enhanced oncogenic potential. Aberrant expression of cellular oncogenes may be due to tumor-specific chromosomal translocations that dysregulate the normal functions of a proto-oncogene. Amplification of cellular oncogenes can also augment their expression by increasing the amount of DNA template available for the production of mRNA. It appears that amplification of certain oncogenes is a common correlate of the progression of some tumours and also occurs as a rare sporadic event affecting various oncogenes in different types of cancer. Amplified copies of oncogenes may or may not be associated with chromosomal abnormalities signifying DNA amplification: double minute chromosomes and homogeneously staining chromosomal regions. Amplified oncogenes, whether sporadic or tumour type-specific, are expressed at elevated levels, in some cases in cells where their diploid forms are normally silent. Increased dosage of an amplified oncogene may contribute to the multistep progression of at least some cancers. (91 Refs)

387. GENE AMPLIFICATION, DRUG RESISTANCE, AND CANCER

Schimke RT

Department of Biological Sciences, Stanford University, California.

Cancer Res; 44(51):1733-42 1984

Keywords (MeSH): Animal; Antineoplastic Agents/therapeutic use; Cell Survival/drug effects; *Drug Resistance; *Gene Amplification; Human; Methotrexate/toxicity; Mice; Neoplasms/drug therapy/*familial and genetic; Neoplasms, Experimental/familial and genetic; Oncogenes; Tetrahydrofolate Dehydrogenase/genetics.

388. DNA SEQUENCE AMPLIFICATION IN MAMMALIAN CELLS (209 Refs)

Hamlin JL, Milbrandt JD, Heintz NH, Azizkhan JC

Department of Biochemistry, University of Virginia School of Medicine, Charlottesville.

Int Rev Cytol; 90:31-82 1984

Keywords (MeSH): Animal; Base Sequence; Comparative Study; DNA Replication; DNA/*genetics/metabolism; Evolution; *Gene Amplification/drug effects; Growth Substances/pharmacodynamics; Human; Neoplasms/familial and genetic; Oncogenes; Review; Sister Chromatid Exchange; Transfection.

389. GENE AMPLIFICATION (22 Refs)

Taira M, Kojima K

Tanpakutsu Kakusan Koso; 29(3):152-63 1984

Keywords (MeSH): Actins/genetics; Animal; Aspartate Carbamoyltransferase/genetics; Carbamyl Phosphate Synthase (Glutamine)/genetics; Colonic Neoplasms/familial and genetic; Drosophila Melanogaster/genetics; Drug Resistance; DNA, Neoplasm/genetics; *Gene Amplification; Hamsters; Human; Leukemia, Myelocytic/familial and genetic; Methotrexate/pharmacodynamics; Multienzyme Complexes/genetics; Proteins/genetics; Rats; Review; Sarcoma, Experimental/familial and genetic/pathology; Tetrahydrofolate Dehydrogenase/genetics.

390. GENE AMPLIFICATION IN EUKARYOTIC CELLS (90 Refs)

Brison O

Institut de Recherches Scientifiques sur le Cancer, Villejuif.

Biochimie; 65(6):III-XI 1983

Keywords (MeSH): Animal; Antineoplastic Agents/pharmacodynamics; Cells/*metabolism; Drug Resistance; DNA/metabolism; Eukaryotic Cells/*metabolism; *Gene Amplification; Human; Neoplasms/familial and genetic; Phenotype; Proteins/biosynthesis; Review.

391. CHROMOSOME ABNORMALITIES AND GENE AMPLIFICATION: COMPARISON OF ANTIFOLATE-RESISTANT AND HUMAN NEUROBLASTOMA CELL SYSTEMS.

Biedler JL, Malera PW, Spengler BA

Chromosomes and Cancer: From Molecules to Man. Rowley JD.

Ullmann JB (Ed.), Academic Press, New York, pp. 117-138, 1983.

392. GENE AMPLIFICATION

Schimke RT

Dept. Biological Sciences, Stanford Univ., Stanford, CA

Gene Amplification. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, 339 pp., 1982.

Gene duplication and amplification studies are reviewed and extended abstracts of a conference on gene amplification are presented. Examples of gene amplification include dihydrofolate reductase gene amplification in murine and Chinese hamster ovary cell lines; in a methotrexate-resistant human leukemia cell line (K562); in rat hepatoma cells; in antifolate-sensitive and -resistant Chinese hamster lung cells; in antifolate-resistant, vincristine-resistant, and human neuroblastoma cells; in reciprocally cross-resistant uptake mutants of neuroblastoma; and in vincristine-resistant Chinese hamster ovary cells. Phenotypic reversion as a consequence of gene amplification, altered regulation of the mouse metallothionein-I gene, amplification of the gene for asparagine synthetase, and control of DHFR DNA replication and messenger RNA production. Other aspects of gene amplification are discussed, including studies involving the SEWA mouse tumor, clonogenic human tumor cells, human small cell lung cancer,

Drosophila, and chicken actin genes during myogenesis. Molecular structures of amplified DNA structures in mouse cell lines and Chinese hamster ovary cells are described and methods for cloning amplified DNA, analysis of CAD gene amplification, and cloning and analysis of double minute DNA are reviewed. Mechanisms of gene amplification are proposed. Chromosomal alterations are discussed with respect to nonrandom gain of chromosomes in human malignant hematologic diseases, a chromosome defect in most cancers, the biologic role for chromatid exchange in mammalian somatic cells, and a common denominator in the tumorigenic action of viral oncogenes and nonrandom chromosomal changes. (295 Refs)

393. GENE-AMPLIFICATION MODEL OF CARCINOGENESIS

Pall ML

*Program in Genetics and Program in Biochemistry/Biophysics,
Washington State Univ., Pullman, WA 99164
Proc Natl Acad Sci USA; 78(4,part2):2465-2468 1981*

A two-stage model of carcinogenesis is proposed based on recent evidence for the occurrence of proto-oncogenes in the vertebrate genome, evidence for gene amplification during carcinogenesis, and studies of the action of tumor promoters. The model is based on the view that an increase in the level of gene product from such proto-oncogenes is sufficient to induce neoplastic transformation. It proposes that the initial step in carcinogenesis (initiation) is a mutation producing a tandem duplication of a proto-oncogene. Gene amplification can then occur by successive unequal sister chromatid crossing-over events in several cell cycles until sufficient gene product is produced to transform the cell. (Author abstract) (54 Refs)

394. AMPLIFIED DIHYDROFOLATE REDUCTASE GENES IN UNSTABLY METHOTREXATE-RESISTANT CELLS ARE ASSOCIATED WITH DOUBLE MINUTE CHROMOSOMES

Kaufman RJ, Brown PC, Schimke RT

*Dept. Pharmacology, Stanford Univ., Stanford, CA 94305
Proc Natl Acad Sci USA; 76(11):5669-5673 1979*

Selection of mammalian cells in progressively increasing concentrations of methotrexate results in selective amplification of DNA sequences coding for dihydrofolate reductase (tetrahydrofolate dehydrogenase, 5,6,7,8-tetrahydrofolate:NADP+ oxidoreductase, EC 1.5.1.3). In some cell variants the amplified genes are stable with growth in the absence of methotrexate, whereas in other variants the amplified genes are lost from the population. We have previously reported that in a stably amplified variant of Chinese hamster ovary cells, the genes are localized to a single chromosome. Herein we report that in mouse S-180 and L5178Y cell lines unstably amplified dihydrofolate reductase DNA sequences are associated with small, paired chromosomal elements denoted 'double minute chromosomes', whereas in stably amplified cells of the same origin, the genes are associated with large chromosomes. (Author abstract) (30 Refs)

395. DOUBLE MINUTE CHROMOSOMES AND THE HOMOGENEOUSLY STAINING REGIONS IN CHROMOSOMES OF A HUMAN NEUROBLASTOMA CELL LINE

Balaban Malenbaum G, Gilbert F

*Dept. Human Genetics, Univ. Pennsylvania Sch. Medicine,
Philadelphia, PA 19174*

Science; 198(4318):739-741 1977

Chromosome banding was used to study four human neuroblastoma cell lines (IMR-32, CHP-134, NMB, and CHP-126). All the lines contained a marker chromosome with a long

nonbanding homogeneously staining region (HSR). The HSR-containing chromosome differed in each line. One line contained two classes of cells, one with an HSR marker chromosome and the other with double minute chromosomes. Each cell had one of these abnormalities, but no cell had both. The presence of two additional chromosomal markers in all cells of this line indicates a common origin. These observations suggest that the double minute chromosomes are derived from the HSR. (19 Refs)

III.

GENERAL REVIEWS OF ONCOGENIC TRANSFORMATION BY ONCOGENE TRANSLOCATION OR AMPLIFICATION

396. EVOLUTION OF TUMOURS AND THE IMPACT OF MOLECULAR ONCOLOGY

Klein G, Klein E

Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.

Nature; 315(6016):190-5 1985

It is generally accepted that tumours arise through the accumulation of several changes affecting the control of cell growth. Recent advances in molecular biology have made it possible to define some of these changes in molecular terms and to trace the steps by which certain tumours evolve. (146 Refs)

397. GENES AND CHROMOSOMES IN HUMAN CANCER (50 Refs)

Yunis JJ

Prog. Med. Virol; 32:58-71 1985

Keywords (MeSH): Chromosome Abnormalities/*complications; Chromosome Deletion; Chromosome Fragile Sites; Chromosome Mapping; Human; Neoplasms/complications/*familial and genetic; Review; Translocation (Genetics).

398. ACTIVATED PROTO-ONC GENES: SUFFICIENT OR NECESSARY FOR CANCER?

Duesberg PH

Department of Molecular Biology, University of California, Berkeley 94720.

Science; 228(4700):665-77 1985

Proto-onc genes are normal cellular genes that are related to the transforming (onc) genes of retroviruses. Because of this relationship these genes are now widely believed to be potential cancer genes. In some tumors, proto-onc genes are mutated or expressed more than in normal cells. Under these conditions, proto-onc genes are hypothesized to be active cancer genes in one of two possible ways: The one gene-one cancer hypothesis suggests that one activated proto-onc gene is sufficient to cause cancer. The multigene-one cancer hypothesis suggests that an activated proto-onc gene is a necessary but not a sufficient cause of cancer. However, mutated or transcriptionally activated proto-onc genes are not consistently associated with the tumors in which they are occasionally found and do not transform primary cells. Further, no set of an activated proto-onc gene and a complementary cancer gene with transforming function has yet been isolated from a tumor. Thus, there is still no proof that activated proto-onc genes are sufficient or even necessary to cause cancer.

399. RELATIONSHIP OF CHROMOSOMAL ALTERATIONS TO GENE EXPRESSION IN CARCINOGENESIS (72 Refs)

Popescu NC, DiPaolo JA
Laboratory of Biology, National Cancer Institute, Bethesda,
Maryland 20205.
Carcinog Compr Surv; 10:419-31 1985

Keywords (MeSH): Cell Transformation, Neoplastic; Chromosome Abnormalities/*familial and genetic; Chromosome Mapping; Gene Amplification; Gene Expression Regulation; Human; Karyotyping; Mutation; Neoplasms/*familial and genetic; Nucleic Acid Hybridization; *Proto-Oncogenes; Review; Sulfites; Translocation (Genetics).

400. TRANSFORMING GENES OF HUMAN MALIGNANCIES (74 Refs)

Aaronson SA, Tronick SR
Laboratory of Cellular and Molecular Biology, National Cancer
Institute, Bethesda, Maryland 20205
Carcinog Compr Surv; 10:35-49 1985

Keywords (MeSH): Cell Cycle; Chromosome Mapping; DNA Replication; Gene Expression Regulation; Guanine Nucleotide Regulatory Protein/genetics; Human; Neoplasms/*familial and genetic; Oncogene Proteins, Viral/*genetics; *Oncogenes; Platelet-Derived Growth Factor/genetics; Protein-Tyrosine Kinase/genetics; Proto-Oncogene Proteins, Cellular/*genetics; *Proto-Oncogenes; Receptors, Endogenous Substances/genetics; Retroviridae/genetics; Review; Translocation (Genetics).

401. ONCOGENES. A POSSIBLE ROLE FOR CANCER GENES IN HUMAN MALIGNANT DISEASE

Haber M, Stewart BW
Children's Leukemia and Cancer Research Unit, Prince of Wales
Children's Hospital, Randwick, NSW.
Med J Aust; 142(7):402-6 1985

A small class of normal cellular genes has the potential to transform cells malignantly. These cellular oncogenes have been identified by their similarity to the transforming genes of oncogenic RNA viruses (retroviruses), and by their ability, under certain circumstances, to transform cells into which they have been transferred. Cellular oncogenes are not normally tumorigenic and, indeed, appear to be critically involved in normal cellular processes, possibly at the level of growth regulation. However, it appears that a number of mechanisms exist whereby these oncogenes can become malignantly activated, leading to uncontrolled cellular proliferation. The evidence implicating cellular oncogenes in human malignant disease is reviewed. (75 Refs)

402. ONCOGENES: THEIR ROLE IN NEOPLASTIC TRANSFORMATION (397 Refs)

Ratner L, Josephs SF, Wong-Staal F
Laboratory of Tumor Cell Biology, National Cancer Institute,
Bethesda, Maryland 20205.
Annu Rev Microbiol; 39:419-49 1985

Keywords (MeSH): Animal; Base Sequence; *Cell Transformation, Neoplastic; Chromosome Mapping; Cloning, Molecular; Gene Amplification; Human; *Oncogenes; Platelet-Derived Growth Factor/physiology; Recombination, Genetic; Review; Translocation (Genetics).

403. ONCOGENES

Gordon H
Department of Medical Genetics, Mayo Clinic, Rochester, MN
55905.
Mayo Clin Proc; 60(10):697-713 1985

Oncogenes were first identified in neoplastic tissues and were thought to be disseminated by retroviruses. They were shown to cause neoplastic transformation of cells in vitro and

were therefore regarded as 'the genes that cause cancer.' They occur in all eukaryotes including humans. More than 30 oncogenes have been identified, and 28 have already been mapped to the human karyotype. When the protein products of the oncogenes were investigated, they were found to be very similar to known substances that are normally involved in the control of cell division - growth factors, plasma-membrane receptors, modulators of the transduction of exogenous signals through the plasma membrane, and nuclear DNA-binding substances. These discoveries changed the original concept of oncogenes. They are now regarded as playing vital roles in the normal control of mitosis, and they should properly be called mitogenes rather than 'oncogenes.' Like all other genes, if a mitogene is mutated, rearranged, translocated, or otherwise deranged, its effects will change; it may then become an oncogene that will promote disorderly cell division and thus contribute to the pathogenesis of cancer. In addition to providing new insights into the normal control of mitosis and its neoplastic transformation, the discovery of the mitogenes has suggested new approaches to the early diagnosis of cancer, to a more rational classification of neoplasms based on pathogenesis rather than morphology, and, perhaps, to more rational forms of therapy. (39 Refs)

404. UICC STUDY GROUP IN BASIC AND CLINICAL CANCER RESEARCH: GENOMIC CHANGES AND THE ORIGIN OF NEOPLASIA

Sager R
Int J Cancer; 35(1):1-4 1985

Keywords (MeSH): Animal; Chromosome Aberrations; Chromosomes/ultrastructure; Corn/genetics; DNA, Bacterial/genetics; DNA, Viral/genetics; *Genes; Genetic Vectors; Human; Neoplasm Metastasis; Neoplasms/*familial and genetic; Oncogenes; Research.

405. MULTIPLE MECHANISMS OF ONCOGENE ACTIVATION IN VIRAL AND NONVIRAL NEOPLASIA

Hayward WS
Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
Life Sci Fed Rep; 30:147-62 1985

Diverse mechanisms for activating the oncogenic potential of a proto-oncogene, based on results observed with the avian leukosis virus (ALV)-induced B cell lymphoma model, are discussed under the following section headings: activation of c-myc by ALV, activation of oncogenes by nonviral neoplasms, regulatory versus structural changes, multistage progression of neoplasia, and somatic selection are discussed. Different proto-oncogenes are activated by different mechanisms, and conversely, similar mechanisms appear to be responsible for activation of the same oncogene in different biological systems. The c-myc gene has been implicated in a wide range of neoplasms. Its activation can occur by such diverse mechanisms as insertion of retroviral regulatory sequences, translocation, and gene amplification, but in each case the mutational event induces a change in gene expression. In contrast, all naturally occurring examples of ras gene activation appear to involve point mutations within the coding sequences of the gene. The myc gene and members of the ras gene family have been implicated in a high proportion of tumors. A possible explanation for this higher than expected frequency is that these genes are more readily activated by single mutational events, or by multiple mutations, each of which confers a selective advantage on the cell. (53 Refs)

406. ONCOGENES AND HUMAN CANCER (177 Refs)

Primentel E
National Center of Genetics, Caracas, Venezuela.
Cancer Genet Cytogenet; 14(3-4):347-68 1985

Keywords (MeSH): Animal; Base Sequence; Cell Transformation; Neoplastic; Cell Transformation, Viral; Chromosome Mapping; Gene Amplification; Gene Expression Regulation; Human; Mutation; Neoplasms/*familial and genetic; *Oncogenes; Review; Transcription, Genetic; Translocation (Genetics).

407. CHROMOSOMAL CHANGES IN CANCERS

Sakaki MS
Radiation Biology Center, Kyoto University.
Gan To Kagaku Ryobo; 11(4):781-8 1984

In addition to the chromosome changes common to cancers, recent development of cytogenetics in human cancers has revealed, the site of specific chromosome changes which characterize specific cancers. Such cancer-specific aberrations are generally reciprocal translocations or deletions, and in some cases the translocations have been unequivocally demonstrated to involve cellular oncogenes (c-onc) in the new transcriptional control of other genes. Chromosome changes relatively common to cancers are amplification of specific genes by chromosome duplication or selective amplification as manifested by double minutes or homogeneously staining regions, and genome reorganization by nondisjunction, somatic recombination, polyploidization-segregation or other parasexual recombinations. The importance of such genome reorganization in cancer development was discussed in relation to the possible involvement of cellular escape mechanisms. (40 Refs)

408. MUTATIONS OF CELLULAR ONCOGENES AS A BASIS FOR NEOPLASTIC CHANGE

Varmus HE
Dept. of Microbiology and Immunology, Univ. of California, San Francisco, CA 94143
Environ Sci Res; 31:61-77 1984

The identification and activation of cellular oncogenes, the relationship of insertional mutagenesis to oncogenesis, the role of proviruses in oncogenesis, and other genetic rearrangements which affect cellular oncogenes are reviewed. Many tumorigenic retroviruses do not carry oncogenes; instead, retroviral proviruses act as insertional mutagens to augment expression of cellular genes. Some activated genes are in the c-onc family, but others, eg, mammary carcinoma induced by the mouse mammary tumor virus, involve proviral insertion mutations that affect cellular genes not represented among retroviral oncogenes. Retroviral DNA is able to activate expression of cellular genes by at least two mechanisms: the provision of a strong viral promoter element for transcription of 'downstream' genes or the indirect action of a viral 'enhancing' element upon cellular sequences competent to serve as transcriptional initiation sites. Translocations occur commonly in tumor cells. Sometimes the break points for the translocations are located nearby and even with c-onc loci, including c-myc. Gene amplification is frequently found in tumor cells. In several human and murine tumor lines the amplified domains have been shown to include c-onc genes that are also expressed at a correspondingly high level, again, with c-myc involvement. DNA from human tumors and tumor cell lines can often transform cultured mouse cells; the transforming activities have been identified in several cases as mutated versions of c-onc's. If a number of mutant genes contribute in concert to tumorigenesis, it may be extremely difficult to determine the function of each mutation in the neoplastic process. (45 Refs)

409. THREE STEPS MUTATION MODEL OF CARCINOGENESIS

De Brackeleer M
University of Calgary, Department of Medical Biochemistry, Alberta, Canada.
Med Hypotheses; 14(4):363-71 1984

Based on recent data, this model supposes that benign and malignant tumors arise when a specific mutation takes place in a specific protein-kinase encoded by a proto-oncogene in a pluripotent stem cell or a committed stem cell. Protein-kinases which are regulated by tissue growth stimulating factors, tissue growth inhibiting factors and differentiating factors phosphorylate specific proteins that can derepress specific genes leading to cell division and cell differentiation. Malignant tumors arise when three mutations happen in a same pluripotent stem cell or committed stem cell: positive mutation at the level of tissue growth stimulating factor; negative mutation at the level of tissue growth inhibiting factor; negative mutation at the level of tissue differentiating factor. Higher expression of oncogenes and amplification reflect the relationship between tumor and host. Chromosomal rearrangements are secondary events that can be important because they may involve genes which are normally not involved in cell division and cell differentiation.

410. THE MOLECULAR BIOLOGY OF CARCINOGENESIS

van der Kamp AW, Jaspers NG
Dept. of Cell Biology and Genetics, Univ. Hosp. Dr.
Molenwaterplein 50, 3015 GE Rotterdam, The Netherlands
Dev Oncol; 25:9-18 1984

Fast transforming RNA retroviruses contain genes for viral replication and a gene or genes that transform host cells, called the viral oncogene (v-onc). Viral oncogenes are homologous to cellular proto-oncogenes (c-onc). Cellular proto-oncogenes also can initiate cell transformation if they are activated, as evidenced by DNA transfection studies in which DNAs from tumor cells were able to transform normal cells; the transformed cells, when inoculated into immunocompromised mice were able, in turn, to give rise to fibrosarcomas. Transforming DNA sequences have thus been identified in human cancers. Human c-onc can also be activated by gene amplification, by single-point mutation, or by transposition. Slowly transforming retroviruses do not contain a v-onc but stimulate expression of a c-onc. Radiation and chemical carcinogens also may activate a c-onc. Expression of multiple c-onc may be involved, as demonstrated in rat embryo fibroblasts transformed by a human bladder carcinoma c-onc. Two groups of oncogenes have been distinguished, one responsible for establishment (immortalization), the other responsible for tumor growth (transformation). The cellular products of these genes are not known, although those of immortalizing genes are found in the nucleus and those of transforming genes are found in the cell membrane. Some oncogenes are homologous to growth factors or enzymes. In melanoma, specific chromosomal translocations occur, but these are not known to involve oncogenes. Random chromosomal translocations have been reported in a family with the Dysplastic Nevus Syndrome. (39 Refs)

411. REPORT ON THE CONFERENCE 'ONCOGENES CELL GROWTH AND CANCER'

Givol D
Fogarty International Center, NIH, Bethesda, MD 20205
Report on the Conference 'Oncogenes Cell Growth and Cancer', Givol D, 1984

A report on the conference 'Oncogenes Cell Growth and Cancer' held at the NIH (November 14-16, 1984) is presented. Sessions were held on the following topics: the ras onco-

genes and malignancy; growth factors, receptors and oncogenes; oncogene activation by chromosomal translocation; steps in cell transformation; and protein kinase in normal and malignant growth. New oncogenes, classification of the oncogenes, cellular functions of oncogenes, mechanisms of malignancy, and prospects for applications are discussed in the report. Several new cellular oncogenes were reported, including oncogene L-myc, identified in small cell lung carcinoma; oncogene met, described in the chemically transformed osteogenic sarcoma line; oncogene neu, isolated from NIH 3T3 foci formed by transfection with DNA from ethylnitrosourea-induced rat neuroblastoma; the gene coding for the well studied tumor-associated antigen p53; and two possible oncogenes, bcl-1 and bcl-2, detected in various B cell leukemias. Four classes of oncogenes were defined: kinase associated, the ras family, nuclear oncogenes and growth factor related. The most telling new information on cellular functions of oncogenes concerns the possible function of c-ras; one ras gene was shown to be essential for the germination of yeast. Serial concepts on the mechanism of malignancy were presented.

412. ONCOGENES AND THE NEOPLASTIC PROCESS

Aaronson SA, Yuasa Y, Robbins KC, Eva A, Gol R, Tronick SR
Lab. of Cellular and Molecular Biology, NCI, Bethesda, MD 20205
Genetic and Phenotypic Markers of Tumors. Aaronson SA, Fratt L, Verna R, eds. New York, Plenum Press, p. 261-77, 1984.

The subject of oncogenes and the neoplastic process is discussed under the following headings: retroviruses as models for studying human cancer, structure of retroviral genomes, transforming genes of acute retroviruses, biological specificity of retroviral oncogenes, cellular origin of retroviral oncogenes, chromosomal localization of onc-related genes in human cells, oncogene activation by chromosomal translocations, isolation of transforming genes from human tumor cells, frequent activation of ras oncogenes in human tumor cells, activation of ras oncogenes by single point mutations, and identification of an oncogene-encoded protein. The research approaches that are discussed have implicated what appears to be a rather limited set of cellular genes as targets for genetic alterations that can lead normal cells to become malignant. These genes were initially detected as transforming genes captured by transforming retroviruses. Independent of retrovirus involvement, they appear to be activated by a variety of mechanisms, including chromosomal rearrangements and even extraordinarily subtle genetic alterations affecting their structure. It is likely that by studying the small set of proto-oncogenes initially discovered as components of a small group of RNA tumor viruses, insight will be gained into strategies that may eventually be useful in the diagnosis, treatment, and even prevention of human cancer. (65 Refs)

413. THE MOLECULAR GENETICS OF CELLULAR ONCOGENES (261 Refs)

Varmus HE
Department of Microbiology and Immunology, University of California, San Francisco.
Annu Rev Genet. 18:553-612 1984

Keywords (MeSH): Animal; B Lymphocytes/ultrastructure; Cell Transformation, Neoplastic/familial and genetic; Cell Transformation, Viral; Chickens; Chromosomes, Human, 21-22; DNA, Neoplasm/genetics; DNA, Viral/genetics; Gene Amplification; Genes, Dominant; Genes, Recessive; Genes, Viral; Human; Immunoglobulins/genetics; Leukemia, Myelocytic/familial and genetic; Mice; Models, Genetic; Mutation; Neoplasms/familial and genetic; *Oncogenes; Rats; Recombination, Genetic; Retroviridae/genetics; Review; Transduction, Genetic; Transformation, Genetic; Translocation (Genetics).

414. ONCOGENES: CLUES TO CARCINOGENESIS

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Department of Cell Biology and Genetics, Erasmus University
Rotterdam, The Netherlands.
Eur J Pediatr. 141(3):134-42 1984

Recent applications of recombinant DNA techniques in cancer research led to the detection of cellular genes with potential transforming activity, called oncogenes (c-onc). Regularly they seem to be involved in normal cell differentiation and proliferation: a number of oncogene-encoded proteins specifically phosphorylate tyrosine, a key reaction in growth control. Certain human tumors exhibit activated forms of these genes and DNA fragments isolated from these neoplasms transform nonneoplastic cells (transfection assay). Oncogenes were first discovered and defined in a number of retroviruses; these viral oncogenes (v-onc) are thought to have been derived from the cellular oncogenes (c-onc). By integration of the v-onc genes into the host genome acute neoplastic transformation of the cell may occur. Several modes of oncogene activation are discussed that lead either to an increased dosage of gene product or to the formation of an altered gene product. The localization of oncogenes in the human genome near the breakpoints of specific chromosome aberrations involved in various neoplasms like Burkitt lymphoma and several leukemias emphasizes the importance of these genes in carcinogenesis. (124 Refs)

415. GENES, CHROMOSOMES, AND CANCER (48 Refs)

Littlefield JW
Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD.
J Pediatr. 104(4):489-94 1984

Keywords (MeSH): Chromosome Aberrations; *Chromosome Abnormalities; Chromosome Deletion; Eye Neoplasms/familial and genetic; Human; Infant; Infant, Newborn; Neoplasms/*familial and genetic; Neuroblastoma/familial and genetic; Neuroblastoma/familial and genetic; *Oncogenes; Oncogenic Viruses/genetics; Retinoblastoma/familial and genetic; Review; Translocation (Genetics).

416. CELLULAR TRANSFORMING GENES AND ONCOGENESIS (102 Refs)

Cooper GM, Lane MA
Laboratory of Molecular Carcinogenesis, Dana-Farber Cancer Institute, Boston, MA.
Biochim Biophys Acta. 738(1-2):9-20 1984

Keywords (MeSH): Animal; Avian Leukosis Viruses/genetics; B Lymphocytes; Bladder Neoplasms/familial and genetic; Breast Neoplasms/familial and genetic; Burkitt's Lymphoma/familial and genetic; Cell Line; *Cell Transformation, Neoplastic; Cell Transformation, Viral; Colonic Neoplasms/familial and genetic; DNA; DNA, Viral; Epstein-Barr Virus/genetics; Fibrosarcoma/familial and genetic; Gene Amplification; Harvey Sarcoma Virus/genetics; Human; Kirsten Sarcoma Virus/genetics; Leukemia, Myelocytic/familial and genetic; Lung Neoplasms/familial and genetic; Lymphoma/familial and genetic; Mammary Cancer Virus/genetics; Neuroblastoma/familial and genetic; *Oncogenes; Review; T Lymphocytes; Transfection; Translocation (Genetics).

417. ONCOGENES - IMPLICATIONS FOR HUMAN CANCER: A REVIEW (45 Refs)

Hall A
Institute of Cancer Research, Chester Beatty Laboratories, London.
J R Soc Med. 77(5):410-6 1984

Keywords (MeSH): Animal; Cats; Cell Line; DNA/genetics; DNA, Recombinant; DNA, Viral/genetics; Gene Expression

Regulation; Genes, Viral; Human; Mice; Neoplasms/etiology/*familial and genetic; *Oncogenes; Oncogenic Viruses/genetics; Rats; Review; RNA, Viral/genetics; Transfection; Translocation (Genetics).

418. ONC GENES AND OTHER NEW TARGETS FOR CANCER CHEMOTHERAPY

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J Cancer Res Clin Oncol; 107(1):1-14 1984

Recent advances in molecular biology have raised the hope that understanding of human cancer might progress rapidly and that improvements in therapy might result (Bishop 1983a, b; Busch 1962; Busch 1976; Duesberg 1983). With the development of gene cloning, DNA sequence analysis and improved hybridization methods, it became possible to evaluate whether cancer results from alteration in gene dosage, point or multiple mutation of genes, translocations, deletions, insertions, inversions, cis or trans altered promoters, amplification, and a variety of other genetic factors, including enhancer elements that alter rates of readouts of particular mRNA species. 'Onc genes' are under intensive study because they offer manageable probes for evaluation of these various possibilities and also because the study of their cellular analogs may further understanding of the molecular biology of normal fetal and malignant cells. Despite the excessive enthusiasm of some proponents of this field and the negativism of its critics (Bishop 1983 a, b; Duesberg 1983), it is clear that analytical tools and new information will be of value in further studies on experimental cancer, regardless of whether cellular oncogenes (c-onc genes) have anything to do with human cancer or not. In the meantime, studies on enzymes, proteins and epitopes involved in growth processes, have opened new avenues for inhibition of human cancer by quantitative reduction of biosynthetic reactions. (144 Refs)

419. HUMAN ONCOGENES

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Hum Genet; 66(2-3):132-42 1984

The information published on human oncogenes up to the fall of 1983 is reviewed. Retroviral oncogenes, proto-oncogenes, and cellular transforming genes are compared. Transforming genes derived from the ras gene family are described in detail. The different mechanisms of activation of proto oncogenes are summarized. Finally, the concerted or sequential action of cellular transforming genes in the multistep process of carcinogenesis is discussed. (88 Refs)

420. ONCOGENES AND RETROVIRUSES (142 Refs)

Tsichida N, Sakuma S

Tanpakushitsu Kakusan Koso; 29(3):219-30 1984

Keywords (MeSH): Animal; Base Sequence; Burkitt's Lymphoma/familial and genetic; Cats; DNA, Neoplasm/genetics; *Genes, Viral; Human; *Oncogenes; Retroviridae/*genetics; Review; Translocation (Genetics).

421. KARYOTYPE EVOLUTION AND TUMOR DEVELOPMENT

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Cancer Genet Cytogenet; 8(2):153-179 1983

The role of mitotic abnormalities in tumor development is discussed. The concept of stem line is considered. Examples of karyotype evolution in the Yoshida sarcoma, Shay's transplantable chloroleukemia, and in the mouse plasma cell

tumor MSPC-1 are presented. Chromosome mutation occurring at the species level is described; such mutations also may occur at the somatic cell level. Thus, the sequential event of chromosome mutations observed in the above tumors might be explained by a similar mechanism of chromosome evolution at the species level. The relationship between karyotype evolution and invasiveness of tumor cells is discussed. A scheme of karyotype evolution in tumor stem line cells is given based on consideration of three events, mutation, selection, and aging or senescence. Nonrandom karyotype change, such as that found in human chronic myelocytic leukemia in the form of the Philadelphia chromosome, is considered. Species differentiation in relation to the evolution of karyotypes and inner chromosome organization and the relation between evolution of inner chromosome organization and development of tumors are discussed. (144 Refs)

422. KARYOTYPIC PROGRESSION IN HUMAN TUMORS

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Cancer Metastasis Rev; 2(3):257-93 1983

Karyotypic progression may be viewed in at least two ways. One approach seeks evidence for increasing and progressive deviation from the normal chromosome pattern in tumors. The clearest examples, found in some leukemias, are those in which successive karyotypic changes are superimposed on an already aberrant cell population. Evidence of chromosomal progression within solid tumors is far less frequent, possibly because the tumors themselves are at a relatively late stage in their evolution. An alternative approach, therefore, attempts to correlate the extent of karyotypic deviation with other aspects of tumor progression. Recent data, based on classical cytogenetic analyses and flow cytometry, are presented to determine relationships between karyotype and specific origin and morphology of tumors. The predominant theme which emerges, not surprisingly, is that the more deviant chromosome patterns are associated with other measures of increased biologic malignancy. What is surprising is the degree to which these properties are expressed in primary tumors and the relative lack of evidence for further karyotypic evolution with recurrence or metastasis. Examples of genetic instability, evolution through polyploidy, gene amplification, and selection for specific chromosomal rearrangement are found in populations of premalignant and malignant human cells. There is increasing recognition of the importance of tumor-specific chromosome aberrations in the stepwise progression from the normal to the fully neoplastic cell. (172 Refs)

423. CANCERS, ONCOGENESIS AND ONCOGENES

Meyer G, Nicoli J

U 119 INSERM - Institut J.-Paoli et J.-Calmettes Marseille.

Med Trop (Mars); 43(3):217-25 1983

The carcinogenic transformation depends on the presence of particular genes, the oncogenes, which are, as a matter of fact, normal cellular genes. The oncogenic retro-viruses are mosaic genomes, transducing oncogenes in the infected cells. These genes are expressed: the product has an activity of protein kinase. The expression is increased in the transformed cells, because the oncogenes are either linked to strong viral promoters in the oncogenic viruses, or translocated in the vicinity of immunoglobulin genes in the case of Burkitt lymphoma. Moreover, there is some modifications (punctual mutations or deletions) of the primary sequence of the protein. (32 Refs)

424. THE IMPLICATIONS OF NONRANDOM
CHROMOSOME CHANGES FOR MALIGNANT
TRANSFORMATION

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59th St., Chicago, IL, 60637

Hematol Blood Transfus; 26:151-155 1981

How and why chromosome changes occur are discussed in relation to malignant transformation. The mechanism for the production of specific, consistent, reciprocal translocations is unknown. A clear difference in preferential break points for chromosome translocations, was observed depending on

whether the rearrangement resulted in a balanced or an unbalanced aberration. Other possible explanations depend on either chromosomal proximity, since translocations may occur more frequently when two chromosomes are close together, or regions of homologous DNA that might pair preferentially and then be involved in rearrangements. Kinds of gene loci that can provide a proliferative advantage during nonrandom changes are considered including the host genome and chromosome changes related to gene dosage (homogeneously staining regions and double minute chromosomes and evidence for gene amplification). (28 Refs)

SUBJECT INDEX

This index is constructed from the National Library of Medicine's Medical Subject Headings (MeSH) which are associated with each abstract included in this publication. These MeSH terms can be used to retrieve similar information from the National Cancer Institute's online database CANCERLINE. The asterisk indicates that the concept indexed is a major point of the article. Bold-faced numbers refer to abstracts which are not indexed with a more specific related term and which may represent articles which are rather more general than the rest. For example: "Carcinogens....2, 17, 39"; where abstracts numbers 2 and 17 would be indexed to a more specific concept under "Carcinogens", such as "Benzo(a)pyrene", but abstract 39 would be indexed only to the level of detail of "Carcinogens".

Keywords	Abstract Numbers	Keywords	Abstract Numbers
Abelson Leukemia Virus.....	122, 127, 128, 138, 143*, 144, 163, 168, 169*, 204, 241, 284*	Amino Acids.....	144, 165, 368
Abnormalities.....	79*, 105, 115*, 121*, 125*, 126*, 129, 131*, 133*, 154*, 170*, 174, 175, 177-179, 187, 209, 210, 221*, 249, 251*-253*, 255, 256*, 261*, 264, 265*, 266*, 285*, 287, 374, 386, 397*, 399*, 415*, 421, 422, 424*	Amino Acids, Cyclic.....	165, 368
Abnormalities, Multiple.....	179, 422	Amnion.....	377
Chromosome Abnormalities.....	79*, 105, 115*, 121*, 125*, 126*, 129, 131*, 133*, 154*, 170*, 174, 175, 177, 178, 187, 209, 210, 221*, 249, 251*-253*, 255, 256*, 261*, 264, 265*, 266*, 285*, 287, 374, 386, 397*, 399*, 415*, 421, 424*	Amylases.....	191*
Acids, Acyclic.....	173	Analgesics.....	249
Acquired Immunodeficiency Syndrome.....	43	Analgesics, Anti-Inflammatory.....	249
Actinomycin.....	64, 270	Anemia.....	179, 234*
Actins.....	389	Anemia, Aplastic.....	179, 234*
Acute Disease.....	126, 242	Aneuploidy.....	380
Acyltransferases.....	180*	Angiotensin I.....	144
Adenocarcinoma.....	93*, 272*, 282*, 283*, 294, 332, 335*, 357, 359*, 363*	Angiotensins.....	144
Adenosine.....	274	Anions.....	399
Adnexa Uteri.....	93, 196, 354, 377	Anthropoidea.....	419
Adnexal Diseases.....	335*	Anti-Inflammatory Agents.....	249, 275
Adolescence.....	98, 125, 137, 141, 164, 320, 326	Anti-Inflammatory Agents, Topical.....	275
Adrenal Cortex Neoplasms.....	352*	Antibiotics.....	64, 270
Adrenal Gland Diseases.....	345*, 346*, 352*	Antibiotics, Antineoplastic.....	64, 270
Adrenal Gland Neoplasms.....	345*, 346*, 352*	Antibodies.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 174, 207*, 215-217, 218*, 219, 222, 223, 243, 255*, 271, 307, 319, 396, 413
Adult.....	118, 123, 125, 137, 140, 141, 147, 148, 149, 152, 156, 157, 162, 164, 181, 184, 190, 202, 210, 218, 220, 221, 222, 225, 240, 248, 255, 269, 281, 283, 298, 326, 335, 336, 349	Agglutinins.....	307
Aged.....	125, 137, 140, 157, 181, 190, 218, 220, 221, 225, 248, 283, 326, 336, 349	Antibodies, Monoclonal.....	174, 243, 271, 319
Middle Age.....	125, 137, 140, 141, 148, 149, 152, 157, 162, 181, 190, 220-222, 248, 269, 281, 283, 326, 335, 349	Antibodies, Neoplasm.....	107*, 174
Age Factors.....	174, 320	Binding Sites, Antibody.....	48, 86, 215
Agglutinins.....	307	Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Aging.....	174, 320, 322	IgA.....	89
Alcohol Oxidoreductases.....	174	IgM.....	34
Alkaloids.....	249	Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Alkylation.....	59, 81, 82, 267, 274, 275	Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Alleles.....	8, 10*, 23, 26, 27, 62, 71, 217, 269, 321, 333*	Immunoglobulin Variable Region.....	48, 86, 215
Amine Oxidoreductases.....	377, 387, 389, 393	Immunoglobulins, Fab.....	48, 86, 215
Amino Acid Metabolism, Inborn Errors.....	252	Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Amino Acid Sequence.....	4, 46, 48, 49, 78, 103, 104, 173, 212, 305, 323, 330, 339, 346, 350, 360-363, 367, 372	Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*,

KEYWORDS	ABSTRACT NUMBERS
100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*	
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Antibodies, Monoclonal.....	174, 243, 271, 319
Antibodies, Neoplasm.....	107*, 174
Antibody Formation.....	117
Antibody Specificity.....	49, 79, 81, 84, 85, 346
Antibody-Producing Cells.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
Antigenic Determinants.....	418
Antigens.....	43, 174, 223, 235*, 236*, 418
Antigens, Neoplasm.....	174, 235*, 236*
Antigens, Surface.....	174, 223
Antigens, Viral.....	43
Antimetabolites.....	387, 389, 394
Antimetabolites, Antineoplastic.....	274*, 387, 389, 394
Antineoplastic Agents.....	64, 270, 274*, 387, 389, 390, 394, 418*
Antiviral Agents.....	243
Arthropods.....	384, 389
Asia.....	419
Asia, Western.....	419
Aspartate Carbamoyltransferase.....	389
Astrocytoma.....	364*
Ataxia Telangiectasia.....	179, 209, 210, 255*
Audio-Visual Aids.....	177
Autoradiography.....	54, 193, 201
Avian Leukosis.....	95*, 297*, 405
Avian Leukosis-Sarcoma Viruses.....	53-56, 118, 122, 212*, 231*, 239, 296*, 297*, 305*, 307*, 362*, 371, 373, 403, 405, 416
Avian Leukosis Viruses.....	53, 54, 55, 56, 118, 122, 212*, 296*, 297*, 305*, 307*, 362*, 371, 405, 416
Erythroblastosis Virus, Avian.....	212*, 362*, 371
Myeloblastosis Virus, Avian.....	53, 56, 118
Avian Sarcoma Viruses.....	231*, 239, 373, 403
Azure Stains.....	248
B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416

KEYWORDS	ABSTRACT NUMBERS
Base Composition.....	98
Base Sequence.....	2, 4, 5, 9, 13, 18, 23, 25-27, 29-31, 33, 34, 36, 39-41, 45, 46, 48, 49, 60, 62-65, 70-74, 76-78, 80, 81, 83-86, 89-91, 95, 96, 98, 99, 103, 104, 113, 122, 131, 132, 148, 150, 151, 158, 159, 161, 173, 193, 194, 196, 200, 201, 203, 212, 213, 215, 217, 219, 228, 250, 258, 271, 292, 293, 298, 305, 307, 309, 313, 316, 321, 323, 327, 329, 330, 339, 340, 345, 346, 350, 353, 360, 361, 363, 367, 371, 372, 375, 378, 379, 383, 386, 388, 401, 402, 403, 406, 408, 418, 420
DNA Insertion Elements.....	62, 193, 203, 250, 258, 408
Repetitive Sequences, Nucleic Acid.....	71, 200, 316, 353, 383, 401
Sequence Homology, Nucleic Acid.....	212, 309, 330, 363
Basophils.....	126
Behavior.....	43
Benzopyrans.....	180
Beta Globulins.....	93
Bibliography.....	257
Biochemical Phenomena.....	2, 4, 5, 9-16, 18, 20, 23, 25-27, 29-31, 33, 34, 36, 37, 39-42, 45, 46, 48, 49, 51-57, 60-65, 68, 70-74, 76-78, 80, 81, 83-86, 89-91, 93, 95, 96, 98, 99, 103, 104, 113, 122, 131, 132, 138, 140, 141, 144, 148-152, 156, 158, 159, 161, 163, 166-168, 170, 171, 173, 176, 187-189, 191-197, 198*, 200, 201, 203, 206*-210*, 211-213, 215, 217, 219, 225, 228, 230*, 232, 233, 236-240, 250, 255*, 268, 270, 271, 278, 280, 288-290, 292-296, 298, 304-309, 313, 316, 318, 321, 323, 326, 327, 329-331, 334, 337, 339, 340, 344-346, 350, 352-359, 360*-362*, 363, 364*-372*, 374, 375, 378, 379, 383, 386, 388, 393, 399-403, 406, 411, 418, 420
Amino Acid Sequence.....	4, 46, 48, 49, 78, 103, 104, 173, 212, 305, 323, 330, 339, 346, 350, 360-363, 367, 372
Base Composition.....	98
Binding Sites.....	48, 86, 93, 206*-210*, 215, 230*, 255*, 344, 359, 360*-362*, 363, 364*-372*, 400, 401, 411
Binding Sites, Antibody.....	48, 86, 215
Receptors, Endogenous Substances.....	93, 230*, 344, 359, 360*-362*, 363, 364*-372*, 400, 401, 411
Guanine Nucleotide Regulatory Protein.....	400
Receptors, Insulin.....	230*
Receptors, Steroid.....	344
Receptors, Immunologic.....	206*-210*, 255*
Genetics, Biochemical.....	2-7, 8*, 9, 10*, 12, 13, 14*, 17*, 18*, 20, 21, 23-25, 26*, 27*, 29-31, 33, 34, 35*-37*, 39*, 40, 41*, 42*, 44*, 45*, 46, 48, 49*, 50, 52*, 58*, 60*-64*, 65-67, 68*, 70, 71*, 72, 73*, 74, 76*, 77, 78, 80, 81, 82*, 83, 84*, 85, 86*, 87-91, 95, 96*, 97*, 98, 99, 100*, 101, 103*, 104*, 105, 106*, 107, 108, 110, 111, 113-115, 118, 122, 123, 128-132, 138*, 139, 142, 144, 146*, 148, 150*, 151, 153, 158*, 159, 161, 162*, 165, 166*, 167*, 169, 172, 173, 176-179, 189, 191-194, 196, 197, 199-201, 203, 204*, 206, 212-215, 216*, 217-219, 224*, 225*, 228, 233-235, 238*, 239, 240*, 243, 245, 250, 252, 258, 260*, 261, 262, 267*, 268, 269, 271*, 272, 273*-275*, 277*-282*, 283, 284*-287*, 288, 289, 290*, 291, 292*-297*, 298, 300, 302, 303*, 304*, 305, 307, 309*-313*, 315*, 316*, 317, 318*-320*, 321-323, 324*-327*, 328, 329*, 330, 331, 332*, 333*, 334, 335*-338*, 339, 340, 341*-343*, 345*, 346*, 348, 349*-352*, 353, 354*-361*, 363, 364*-366*, 367, 368*, 369*, 370, 371*, 372*, 373, 375, 376, 377*-379*, 381, 382*, 383, 384*-390*, 392*-394*, 396, 399-403, 405-411, 413, 416-420, 422, 423
Base Sequence.....	2, 4, 5, 9, 13, 18, 23, 25-27, 29-31, 33, 34, 36, 39-41, 45, 46, 48, 49, 60, 62-65, 70-74, 76-78, 80, 81, 83-86, 89-91, 95, 96, 98, 99, 103, 104, 113, 122, 131, 132, 148, 150, 151, 158, 159, 161, 173, 193, 194, 196, 200, 201, 203, 212, 213, 215, 217, 219, 228, 250, 258, 271, 292, 293, 298, 305, 307, 309, 313, 316,

KEYWORDS

ABSTRACT NUMBERS

- 321, 323, 327, 329, 330, 339, 340, 345, 346, 350, 353, 360, 361, 363, 367, 371, 372, 375, 378, 379, 383, 386, 388, 401, 402, 403, 406, 408, 418, 420
- DNA Insertion Elements..... 62, 193, 203, 250, 258, 408
- Repetitive Sequences, Nucleic Acid..... 71, 200, 316, 353, 383, 401
- Sequence Homology, Nucleic Acid..... 212, 309, 330, 363
- Cloning, Molecular..... 4, 7, 33, 36*, 37, 44*, 46, 62, 63, 71-73, 86*, 99, 101, 104*, 148, 150*, 159, 161, 169, 189, 192, 193, 197, 203, 204, 214, 216*, 217, 224*, 225*, 233, 235, 239, 271, 321, 329*, 334, 339, 340, 343, 346*, 361, 367, 369, 375, 383, 393, 402
- DNA Repair..... 179
- DNA Replication..... 100*, 384, 386, 388, 400
- Gene Expression Regulation..... 3, 4, 7, 8*, 17*, 21, 24, 26*, 27*, 40, 45, 50, 52*, 53*, 62*, 63, 64*, 66, 74, 76*, 78, 82*, 87, 88, 95, 96*, 97*, 106*, 108, 110, 111, 114, 115, 118, 123, 128, 129, 131, 138*, 144, 153, 159, 162, 165, 166*, 167*, 169, 172, 178, 179, 199-201, 204*, 206, 245, 250, 252, 260*, 261, 262, 267*, 268, 271*, 272, 273*, 274*, 277*-281*, 282*, 283, 284*, 285*, 286*, 287*, 288, 289, 290*, 291, 292*-294*, 295*, 296*, 297*, 298, 300, 302, 303*, 304*, 309*, 310*-313*, 315*, 316*, 317, 318*, 319*, 320*, 322, 324*, 325*, 326*, 327*, 328, 329*, 330, 331, 332*, 333*, 334, 335*, 336*, 337*, 338*, 339, 341*, 342*, 343*, 345*, 346*, 349*-352*, 353, 354*, 356*, 357*, 358*, 359*, 361*, 363, 364*-366*, 367, 368*, 370, 371*, 372*, 373, 375-377, 378*, 379*, 381, 382*, 383, 384*, 385*, 386*, 387*-390*, 392*-394*, 396, 399, 400, 402, 403, 405, 406, 407, 408-411, 413, 416, 417, 419, 422, 423
- Dosage Compensation (Genetics)..... 422
- Gene Amplification..... 115, 129, 159, 166*, 167*, 169, 250, 260-262, 267*, 268, 271*, 272, 273*, 277*-282*, 283, 284*-287*, 288-291, 292*-296*, 298, 302, 303*, 304*, 309*-313*, 315*, 316*, 319*, 320*, 322, 324*-327*, 328, 329*, 330, 331, 332*, 333*, 334, 335*-338*, 339, 341*-343*, 345*, 346*, 349*-352*, 353, 354*, 356*, 357*, 358, 359*, 361*, 363, 364*-366*, 367, 368*, 370, 371*, 372*, 373, 375-377, 378*, 379*, 381, 382*, 383, 384*-390*, 392*-394*, 399, 402, 403, 406, 407, 411, 413, 416, 419, 422
- Genes, Regulator..... 4, 7, 8*, 26*, 27*, 40, 45, 62*, 64, 66, 76*, 96*, 405, 411
- Enhancer Elements (Genetics)..... 4, 7, 27, 62*
- Promoter Regions (Genetics)..... 64, 66, 76*
- RNA Processing, Post-Transcriptional..... 64*
- Genes, Structural..... 14*, 17, 18, 24, 33, 35*, 37*, 40, 48, 50, 61*, 67, 68*, 71*, 74, 78, 82, 86*, 100, 107, 118, 131, 191, 206, 218, 238*, 240*, 289, 305, 360*, 366, 369*, 370, 372*, 377*, 405
- Genetic Code..... 89, 410
- Transcription, Genetic..... 3, 5-7, 10*, 12, 17, 18*, 20, 21, 27, 29, 37*, 39*, 41*, 42*, 44, 45*, 46, 49*, 50, 60*, 63*, 64*, 73*, 76*, 81, 82, 84*, 85, 89, 95, 96*, 103-105, 108, 113, 123, 130, 139, 142, 146*, 150*, 158*, 162*, 166, 176, 177, 199, 201, 212, 216, 217, 233, 234, 243, 269, 271, 275*, 279, 280, 290, 292*, 295, 296, 333*, 337, 345, 348, 352, 355*, 403, 406, 408, 411
- RNA Processing, Post-Transcriptional..... 64*
- Translation, Genetic..... 103*, 104, 197, 272, 300, 305, 345, 403
- Molecular Conformation..... 198*, 219, 367
- Nucleic Acid Hybridization..... 2, 10-16, 20, 23, 27, 31, 34, 36, 37, 39-42, 51-57, 60, 61, 64, 68, 73, 76, 84-86, 89, 93, 94, 138, 140, 141, 148-150, 152, 156, 158, 159, 161, 163, 166-168, 170, 171, 176, 187-189, 191-195, 197, 201, 203,

KEYWORDS

ABSTRACT NUMBERS

- 207, 209, 211, 213, 225, 228, 230, 232, 233, 236-240, 270, 271, 278, 280, 288-290, 293-296, 304, 306, 308, 316, 318, 326, 327, 331, 334, 337, 346, 352-359, 364, 366, 370-372, 374, 393, 399
- Nucleic Acid Renaturation..... 268, 316
- Protein Binding..... 26
- Substrate Specificity..... 144
- Biochemistry..... 221, 344
- Biological Factors..... 108, 139, 144, 183*, 191*, 270, 307, 364, 365*, 368, 369*, 371, 372, 388, 400-403, 410-412
- Growth Substances..... 108, 139, 183*, 191*, 270, 364, 365*, 368, 369*, 371, 372, 388, 400, 401, 402, 403, 410, 411, 412
- Epidermal Growth Factor-Urogastrone..... 364, 365*, 368, 369*, 371, 372
- Nerve Growth Factors..... 191*
- Platelet-Derived Growth Factor..... 139, 183*, 400, 402, 403, 412
- Mitogens..... 307
- Slow-Reacting Substances..... 144
- Biological Phenomena..... 58, 95, 105, 108, 110, 114, 124, 127, 132, 165*, 179, 200*, 201, 233, 236, 284, 296*, 297, 300, 305*, 314, 321, 331, 340, 373*, 377, 388, 396, 401, 406, 410, 411, 413, 416, 417, 419, 421*, 423
- Evolution..... 388, 401, 421*
- Microbiologic Phenomena..... 58, 95, 105, 108, 110, 114, 124, 127, 132, 165*, 179, 200*, 201, 233, 236, 284, 296*, 297, 300, 305*, 314, 321, 331, 340, 373*, 377, 388, 396, 401, 406, 410, 411, 413, 416, 417, 419, 423
- Cell Transformation, Viral..... 95, 108, 120, 114, 132, 165*, 179, 236, 284, 296*, 297, 305*, 373*, 396, 401, 406, 413, 416, 419, 423
- Inclusion Bodies, Viral..... 200*
- Transfection..... 58, 105, 124, 201, 233, 296, 300, 314, 321, 331, 340, 373, 377, 388, 410, 411, 416, 417
- Virus Replication..... 127, 419
- Biological Products..... 307
- Bird Diseases..... 95*, 297*, 405
- Birds..... 122, 212, 296, 297, 301, 358, 363, 392, 398, 413, 419
- Poultry..... 122, 212, 296, 297, 301, 358, 363, 392, 398, 413, 419
- Chickens..... 122, 212, 296, 297, 301, 358, 363, 392, 398, 413, 419
- Bladder Diseases..... 190*, 194*, 259*, 340, 351*, 416
- Bladder Neoplasms..... 190*, 194*, 259*, 340, 351*, 416
- Blood..... 5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 126, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 234, 251, 253, 289, 298, 351, 396, 413, 416
- Blood Cells..... 5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 126, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 234, 251, 253, 289, 298, 351, 396, 413, 416
- Erythrocytes..... 174
- Leukocytes..... 5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 126, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 234, 251, 253, 289, 298, 351, 396, 413, 416

KEYWORDS

ABSTRACT NUMBERS

Granulocytes.....	126, 174, 298
Lymphocytes.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 251, 253, 289, 396, 413, 416
B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 356, 413, 416
T Lymphocytes.....	33*, 79, 92*, 94, 125, 174, 206-208, 215, 221*, 222, 233, 253, 416
Monocytes.....	234
Blood Physiology.....	183, 234*
Blood Protein Disorders.....	30, 57, 201, 248*
Blood Proteins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 139, 170*, 183*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 400, 402, 403, 412, 413
Immunoproteins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 96*, 98*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*

KEYWORDS

ABSTRACT NUMBERS

120, 170*	
Paraproteins.....	82
Platelet-Derived Growth Factor.....	139, 183*, 400, 402, 403, 412
Serum Globulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Beta Globulins.....	93
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Bloom Syndrome.....	179
Body Constitution.....	79, 127
Bone Marrow.....	141, 234, 243, 248, 270, 299
Bone Marrow Cells.....	174, 183, 245*, 270*
Bone Marrow Diseases.....	100, 116, 121, 126, 129, 133, 134, 138*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 234*, 242, 243, 245*, 246*, 251, 253, 298*, 302*, 348*, 359, 386, 389, 407, 413, 416
Anemia, Aplastic.....	179, 234*
Myelodysplastic Syndromes.....	116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*,

KEYWORDS

ABSTRACT NUMBERS

178, 182*, 183*, 186*, 242, 243, 245*, 246*, 251, 253, 298*, 302*, 359, 386, 389, 407, 413, 416	
Leukemia, Myelocytic.....	10, 12, 104, 115, 116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 298*, 302*, 307*, 308*, 310, 318, 356*, 399, 374*, 386, 389, 407, 413, 416
Leukemia, Myeloblastic.....	10, 12, 104, 115, 116, 121, 133, 134, 146*, 166*, 174*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 307*, 308*, 310, 318, 356*, 374*
Myeloproliferative Disorders.....	100, 134, 138*, 348*
Brain.....	322
Brain Diseases.....	179, 209, 210, 252, 255*, 310, 370*
Brain Diseases, Metabolic.....	252
Brain Neoplasms.....	310, 370*
Breast Diseases.....	272*, 279*, 295*, 338*, 344*, 359, 361*, 365*, 381*, 416
Breast Neoplasms.....	272*, 279*, 295*, 338*, 344*, 359, 361*, 365*, 381*, 416
Bronchial Neoplasms.....	273*
Burkitt's Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Bursa of Fabricius.....	122, 297
C-Type Viruses.....	119
Carbamyl Phosphate Synthase (Glutamine).....	389
Carbohydrate Dehydrogenases.....	174
Carboxylic Acids.....	173
Carboxylic Ester Hydrolases.....	407
Carcinogens.....	69*, 127*, 180*, 193*, 250, 264, 275, 286, 386, 407, 419, 423
Croton Oil.....	275
Dimethylhydrazines.....	286
Nitrosamines.....	180*
Carcinoma.....	110, 180*, 190*, 264, 267*, 273*, 276*, 277*, 283*, 292*, 299*, 309*, 310, 330*, 331*, 332, 336*, 349*, 350, 355*, 359, 362, 363, 367*-369*, 371, 372, 396
Carcinoma, Mucinous.....	283*
Carcinoma, Oat Cell.....	110, 267*, 276*, 277*, 292*, 299*, 309*, 310, 330*, 332, 350, 355*, 396
Carcinoma, Squamous Cell.....	180, 273*, 332, 336*, 349*, 359, 362, 367*-369*, 371, 372
Carcinoma, Transitional Cell.....	190*
Carcinoma, Bronchogenic.....	273*
Carcinoma, Renal Cell.....	93*
Carnivora.....	99, 354, 417, 419, 420
Carotenoids.....	317*, 318*
Carrier Proteins.....	93, 400
Cat Diseases.....	99*
Cathartics.....	127, 128
Cations.....	319
Cations, Monovalent.....	319
Cats.....	99, 417, 419, 420
Cebidae.....	419
Cell Cycle.....	12, 15, 54,

KEYWORDS

ABSTRACT NUMBERS

61, 73, 108*, 167, 179, 182, 183, 185, 197, 205, 213, 239, 260, 270, 274, 285, 341, 347, 364, 365, 368, 386, 393, 400, 409, 411*, 418	
Cell Division.....	12, 15, 54, 61, 73, 108*, 167, 179, 182, 183, 185, 197, 205, 213, 239, 260, 270, 274, 285, 341, 347, 364, 365, 368, 386, 393, 409, 411*, 418
Cell Division Phases.....	15, 54, 61, 167, 182, 185, 197, 205, 213, 239, 285, 347
Metaphase.....	15, 54, 61, 167, 182, 185, 197, 205, 213, 239, 285, 347
Meiosis.....	54
Mitosis.....	260, 306
Cell Differentiation.....	5, 10, 12, 114, 118, 174, 217, 245, 270, 274, 317, 318, 384, 409
Cell Fusion.....	101, 260, 347
Cell Line.....	1-5, 7, 10-12, 14, 16, 18, 20, 23, 25, 26, 29, 34, 35, 37-39, 42-44, 47, 49, 51, 52, 58, 60-62, 64, 70-73, 75, 76, 80, 81, 83, 86, 89, 93, 94, 100, 103, 104, 107, 115, 138, 143, 145, 146, 158, 166, 167, 184, 186, 192, 197-199, 211, 213, 214, 216, 218, 222, 223, 225, 233, 234, 236, 238, 259, 267, 268, 270, 271, 274-280, 284, 285, 287-289, 293, 295-297, 299-304, 306-309, 311-314, 316-319, 323-327, 329, 331, 335, 337, 338, 342, 343, 345-347, 350, 352, 354-358, 360-362, 364-369, 371, 372, 377, 379, 385, 386, 394, 401, 411, 416, 417, 419, 421
Hela Cells.....	146, 301
L Cells.....	76, 192
Cell Nucleus.....	1*, 3, 4*, 5, 6, 8*-10*, 13, 14*-16*, 19, 20*, 23, 24, 25*, 26*, 27*, 28*, 30*, 31*, 35*, 38*, 39, 40*, 41, 42*, 43, 45, 50, 52, 53, 54*-57*, 60*, 83, 91, 93*, 94*, 97, 98*, 102, 104, 107, 109, 111, 116, 117, 119, 120, 123, 125, 126*, 128, 129, 133, 134, 137, 138*, 140*, 141*, 142, 145, 146*-149*, 151*-156*, 158*, 159, 160*, 161*, 162, 164*, 167*-171*, 172, 174, 176*, 177, 178, 181*-186*, 188*, 189, 190*, 191*, 193*-197*, 202*, 205*, 206*, 207, 209-211, 212*-221*, 223*-232*, 234*-241*, 244, 246, 247*, 249*, 251, 253-255, 257*, 258, 261, 264*, 266, 267, 273*, 278, 279, 281, 287, 288, 289*, 298, 300, 302*, 306, 313, 328*, 330*, 346, 347*, 352, 357, 360, 366*-368*, 374*, 380-382, 384, 394*, 403, 404, 407, 413, 418, 422
Cell Nucleolus.....	418
Chromatin.....	8*-10*, 26*, 27*, 60*, 253, 267, 275*
Chromosomes.....	1*, 3, 4*, 5, 6, 13, 14*-16*, 19, 20*, 23, 24, 25*, 28*, 30*, 31*, 35*, 38*, 39, 40*, 41, 42*, 43, 45, 50, 52, 53, 54*-57*, 83, 91, 93*, 94*, 97, 98*, 102, 104, 107, 109, 111, 116, 117, 119, 120, 123, 125, 126*, 128, 129, 133, 134, 137, 138*, 140*, 141*, 142, 145, 146*, 147*, 148*, 149*, 151*-156*, 158*, 159, 160*, 161*, 162, 164*, 167*-171*, 172, 174, 176*, 177, 178, 181*-186*, 188*, 189, 190*, 191*, 193*-197*, 202*, 205*, 206*, 207, 209-211, 212*-221*, 223*-232*, 234*-241*, 244, 246, 247*, 249*, 251, 254, 255, 257*, 258, 261, 264*, 266, 278, 279, 281, 287, 288, 289*, 298, 302*, 306, 313, 328*, 330*, 346, 347*, 352, 357, 360, 366*-368*, 374*, 380-382, 384, 394*, 403, 404, 407, 413, 422
Chromosomes, Human.....	1*, 3, 4*, 5, 6, 13, 14*-16*, 19, 20*, 23, 24, 25*, 28*, 30*, 31*, 35*, 38*, 39, 40*, 41, 42*, 43, 45, 50, 52, 53, 54*-57*, 91, 93*, 94*, 97, 98*, 102, 104, 107, 109, 111, 116, 117, 119, 120, 123, 125, 126*, 129, 133, 134, 137, 140*, 141*, 142, 145, 146*-149*, 151*-156*, 158*, 159, 160*, 161*, 162, 164*, 167*-171*, 172, 174, 176*, 177, 178, 181*-186*, 188*, 189, 190*, 191*, 193*-197*, 202*, 205*, 206*, 207, 209-211, 212*, 213*, 214*-221*, 223*-232*, 234*-241*, 244, 246, 247*, 249*, 251, 254, 255, 257*, 258, 261, 264*, 266, 278, 279, 281, 287, 288, 289*, 298, 302*, 306, 313, 328*, 330*, 346, 347*, 352, 357, 360, 366*-368*, 374*, 380-382, 403, 407, 413, 422
Chromosomes, Human, 1-3.....	1, 14*-16*, 19,

KEYWORDS

ABSTRACT NUMBERS

- 25*, 28, 93*, 111, 120, 125, 129, 133, 164*, 189, 190*, 191*, 193*, 229*, 239*, 247*, 255, 278, 313, 328*, 330*, 357, 381, 382
- Chromosomes, Human, 13-15..... 1, 3, 4*, 5, 19, 20*, 38*, 39, 40*, 41, 45, 50, 57*, 91, 94*, 97, 98*, 102, 107, 109, 111, 117, 119, 120, 123, 125, 129, 133, 181*, 206*, 207, 210, 215*-221*, 223*-225*, 227, 238*, 240*, 241*, 244, 246, 255, 258, 261, 266, 374, 380
- Chromosomes, Human, 16-18..... 23, 111, 123, 125, 133, 188, 214*-217*, 224*, 226*-228*, 232*, 235*-238*, 240*, 244, 254, 266, 288, 360
- Chromosomes, Human, 19-20..... 50, 164*, 229*-231*, 239*
- Chromosomes, Human, 21-22..... 1, 19, 24, 28, 42*, 43, 111, 116, 120, 123, 126, 133, 134, 137, 140*, 145, 146*-149*, 151*, 153*-155*, 158*, 159, 160*, 161*, 162, 164*, 167*-171*, 176*, 177, 178, 181*-186*, 188*, 195*, 196*, 211, 212*, 244, 246, 251, 261, 266, 298, 407, 413, 422
- Chromosomes, Human, 4-5..... 156, 234*, 281, 288
- Chromosomes, Human, 6-12..... 1*, 3, 4*, 5, 13, 14*, 16*, 19, 20*, 23, 24, 25*, 28*, 31*, 35*, 38*, 39, 40*, 41, 42*, 43, 50, 52, 53, 54*-56*, 91, 93*, 97, 98*, 102, 104, 107, 109, 111, 117, 119, 120, 123, 125, 129, 133, 137, 140, 141*, 142, 147, 149, 151*, 152*, 154, 156*, 158*, 160*, 162, 168*, 169*, 171*, 172, 174, 176, 177, 184*, 186*, 189, 190*, 193*-195*, 196, 197*, 202*, 206*, 209-211, 212*, 213*, 218*, 219*, 223*, 241*, 246, 266, 288, 289*, 302*, 306, 357, 366*-368*, 374*, 381
- Nucleolus Organizer Region..... 138*
- Sex Chromosomes..... 249, 254, 306
- Cell Physiology..... 5, 6, 10, 12*, 15, 22, 31, 32, 33*, 51*, 54, 61, 73, 75*, 80, 81, 92*, 95, 101*, 108*, 114, 116, 118, 131, 132, 134, 135*, 137, 166-168, 173, 174, 179, 182, 183, 185, 197, 199*, 204, 205, 213, 215, 217, 221*, 233*, 239, 245*, 250, 260, 263*, 265, 270, 274, 285, 296*, 297, 299, 308*, 314*, 317, 318, 321*, 331, 336, 339, 341, 342*, 347, 350*, 364, 365, 368, 382*, 384-387, 393*, 398-401, 402*, 403, 405, 406, 408*, 409, 410*, 411*, 412, 413, 414*, 416*, 418, 419, 423, 424*
- Cell Cycle..... 12, 15, 54, 61, 73, 108*, 167, 179, 182, 183, 185, 197, 205, 213, 239, 260, 270, 274, 285, 341, 347, 364, 365, 368, 386, 393, 400, 409, 411*, 418
- Cell Division..... 12, 15, 54, 61, 73, 108*, 167, 179, 182, 183, 185, 197, 205, 213, 239, 260, 270, 274, 285, 341, 347, 364, 365, 368, 386, 393, 409, 411*, 418
- Cell Division Phases..... 15, 54, 61, 167, 182, 185, 197, 205, 213, 239, 285, 347
- Metaphase..... 15, 54, 61, 167, 182, 185, 197, 205, 213, 239, 285, 347
- Meiosis..... 54
- Mitosis..... 260, 386
- Cell Differentiation..... 5, 10, 12, 114, 118, 174, 217, 245, 270, 274, 317, 318, 384, 409
- Cell Fusion..... 101, 260, 347
- Cell Survival..... 299, 341, 387
- Cell Transformation, Neoplastic..... 6, 12*, 22, 31, 32, 33*, 51*, 75*, 80, 81, 92*, 95, 101*, 108, 116, 131, 132, 134, 135*, 137, 166, 168, 173, 179, 199*, 204, 215, 221*, 233*, 239, 245*, 250, 263*, 265, 296*, 297, 299, 308*, 314*, 321*, 331, 336, 339, 342*, 350*, 382*, 385, 393*, 398, 399, 401, 402*, 403, 405, 406, 408*, 410*, 411*, 412, 413, 414*, 416*, 419, 423, 424*
- Cell Transformation, Viral..... 95, 108, 110, 114, 132, 165*, 179, 236, 284, 296*, 297, 305*, 373*, 396, 401, 406, 413, 416, 419, 423
- Cells, Cultured..... 1-7, 10-12, 14-16,

KEYWORDS

ABSTRACT NUMBERS

- 17*, 18, 20, 23, 25, 26, 29, 34, 35, 37-39, 42-44, 47, 49, 51-53, 56-58, 60-62, 63, 64, 67, 70-73, 75, 76, 80, 81, 85, 86, 87*, 89, 93, 94, 100, 103, 104, 107, 110, 114, 115, 117, 118, 137, 138, 142*, 143, 145, 146, 158, 166-168, 170, 171, 176, 179, 183, 184, 185, 186, 191, 192, 197, 198, 199*, 207, 209, 211, 213, 214, 216, 218, 222-225, 230, 231, 233, 234, 236, 238, 241, 259, 260*, 267, 268, 270, 271, 274-280, 284, 285, 287-289, 293, 295-297, 299-304, 306, 307, 308, 309, 311-313, 314, 316-319, 321, 323-326, 327, 329, 331, 335, 337, 338, 341, 342, 343, 345, 346, 347*, 350, 352, 354-358, 360-362, 364-369, 371, 372, 373, 377, 378, 379, 385, 386, 394*, 396, 401, 411, 416, 417, 419, 421
- Cell Line..... 1-5, 7, 10-12, 14, 16, 18, 20, 23, 25, 26, 29, 34, 35, 37-39, 42-44, 47, 49, 51, 52, 58, 60-62, 64, 70-73, 75, 76, 80, 81, 85, 86, 89, 93, 94, 100, 103, 104, 107, 115, 138, 143, 145, 146, 158, 166, 167, 184, 186, 192, 197-199, 211, 213, 214, 216, 218, 222, 223, 225, 233, 234, 236, 238, 259, 267, 268, 270, 271, 274-280, 284, 285, 287-289, 293, 295-297, 299-304, 306-309, 311-314, 316-319, 323-327, 329, 331, 335, 337, 338, 342, 343, 345-347, 350, 352, 354-358, 360-362, 364-369, 371, 372, 377, 379, 385, 386, 394, 401, 411, 416, 417, 419, 421
- Hela Cells..... 146, 301
- L Cells..... 76, 192
- Clone Cells..... 37, 51, 85, 87*, 110, 146, 185, 199*, 301, 347, 368, 386, 396
- Hela Cells..... 146, 301
- Hybridomas..... 87*, 199*
- Hybrid Cells..... 3, 5, 6, 15, 17*, 18, 20, 37, 38, 51, 53, 56, 57, 67, 87*, 114, 117, 118, 137, 142*, 168, 170, 171, 176, 179, 191, 192, 199*, 207, 209, 211, 218, 224, 225, 230, 231, 234, 236, 241, 260*, 347*, 366
- Hybridomas..... 87*, 199*
- Cellular Inclusions..... 200*
- Cellulose..... 344
- Central Nervous System..... 322
- Central Nervous System Diseases..... 179, 181*, 209, 210, 252, 255*, 310, 370*
- Cereals..... 404
- Cerebellar Ataxia..... 179, 209, 210, 255*
- Cerebellar Diseases..... 179, 209, 210, 255*
- Cervix Diseases..... 349*
- Cervix Neoplasms..... 349*
- Cheek..... 180
- Chemistry..... 47, 52, 57, 59, 81, 82, 143, 144, 146, 158, 162, 173, 201, 267, 274, 275, 282, 290, 295, 301, 337, 344, 351, 355, 366, 376, 378
- Biochemistry..... 221, 344
- Chemistry, Analytical..... 47, 52, 57, 143, 162, 201, 282, 290, 295, 337, 344, 351, 366, 376, 378
- Chemistry, Organic..... 59, 81, 82, 143, 144, 173, 267, 274, 275
- Chemistry, Physical..... 47, 52, 57, 143, 144, 146, 158, 162, 201, 282, 290, 295, 301, 337, 344, 351, 355, 366, 376, 378
- Electrochemistry..... 47, 52, 57, 143, 162, 201, 282, 290, 295, 337, 344, 351, 366, 376, 378
- Electrophoresis..... 47, 52, 57, 143, 162, 201, 282, 290, 295, 337, 344, 351, 366, 376, 378
- Electrophoresis, Agar Gel..... 52, 162, 201, 282, 290, 295, 337, 351, 366, 376, 378
- Electrophoresis, Polyacrylamide Gel..... 47, 57, 344
- Immunoelectrophoresis..... 143
- Molecular Conformation..... 198*, 219, 367
- Molecular Weight..... 144, 146, 158, 201, 301, 351, 355
- Chickens..... 122, 212, 296,

KEYWORDS

ABSTRACT NUMBERS

297, 301, 358, 363, 392, 398, 413, 419	
Child.....	125, 137, 153,
156, 184, 269, 315, 320, 326, 415	
Child, Preschool.....	125, 137, 156,
184, 315, 320, 326	
Chimera.....	145, 149*
Chromatin.....	8*-10*, 26*, 27*,
60*, 253, 267, 275*	
Chromosome Aberrations.....	1*, 2, 3,
4*-6*, 7, 8, 9*, 13*-20*, 22*, 23, 24, 25*, 26, 27*, 28, 29*-31*,	
32, 33, 34*, 35*, 37*-39*, 40, 41, 42*, 44*, 45, 46*, 47*, 48, 49*,	
50, 51*, 52*, 53*, 54*-57*, 58, 59, 60*-63*, 64, 65*-69*, 70, 71*-	
79*, 80, 81, 82, 83*-85*, 87*-89*, 91, 92, 93*, 94-97, 98*, 102*,	
103*, 106, 107*, 108-110, 111*, 112*, 113*, 114, 115*-117*,	
118*, 119*, 120*, 122, 123*, 124, 125, 126*, 127*, 128, 129*,	
131*-133*, 134*, 135*, 136*, 137*, 138*, 139, 140, 141*, 142*,	
144, 145, 147*, 148, 149*, 151*-153*, 154-156, 157*-162*, 164*,	
168-170, 171*, 172*, 173, 174*, 175-177, 179*, 181*, 182, 183*-	
186*, 188, 190, 192, 195*, 196*, 197, 202, 203, 205, 206*, 207,	
208, 211*, 214*-219*, 220*, 221, 222*, 223, 224*, 225*, 226-228,	
229*, 230, 234*, 235, 238*, 239, 240*, 242*, 243*, 244*, 245,	
246*, 247*, 248*, 249, 250, 251-253, 254*, 255*, 256, 257, 258*,	
259*, 260, 261, 262*, 263*, 264-266, 281*, 288, 292*, 306*, 312,	
328, 336, 360, 366*, 367, 368*, 371, 374, 380*-382*, 385, 386,	
393, 396-402, 404, 405, 406, 407*, 409, 410-413, 414, 415, 416,	
417, 418, 419-421, 422*, 424*	
Aneuploidy.....	380
Chromosome Deletion.....	62, 110, 155,
190, 203, 234*, 242, 251, 258, 261, 265, 380, 396, 397, 401,	
415	
Chromosome Fragile Sites.....	157, 179, 248,
253, 254*, 255*, 264, 312, 397	
Inversion (Genetics).....	61
Translocation (Genetics).....	1*, 2, 3,
4*-6*, 7, 8, 9*, 13*-20*, 22*, 23, 24, 25*, 26, 27*, 28, 29*-31*,	
32, 33, 34*, 35*, 37*-39*, 40, 41, 42*, 44*, 45, 46*, 47*, 48,	
49*, 50, 51*, 52*, 53*, 54*-57*, 58, 59, 60*-63*, 64, 65*-69*,	
70, 71*-79*, 80-82, 83*-85*, 87*-89*, 91, 92, 93*, 94-97, 98*,	
102*, 103*, 106, 107*, 108-110, 111*-113*, 114-116, 117*-	
120*, 122, 123*, 124, 125, 126*, 127*, 128, 129*, 131*-133*,	
134, 135*, 136, 137*, 138*, 139, 140, 141*, 142*, 144, 145,	
147*, 148, 149*, 151*-153*, 154-156, 157*-162*, 164*, 168-	
170, 171*, 172*, 173, 174*, 175-177, 181*, 182, 183*-186*,	
188, 192, 195*, 196*, 197, 202, 206*, 207, 208, 211*, 214*-	
219*, 221-223, 224*, 225*, 226-228, 229*, 230, 235, 238*, 239,	
240*, 242, 243, 244*, 245, 246*, 247, 249, 251-253, 255*, 256,	
258*, 261, 263-266, 288, 292*, 306*, 328, 366*, 367, 368*, 371,	
374, 380, 385, 386, 396-402, 405-407, 409-413, 415-417, 419-	
422, 424*	
Philadelphia Chromosome.....	137*, 139, 141*,
142, 148, 149*, 152*, 157*, 172*, 174*, 242, 246, 253	
Trisomy.....	37, 129, 136,
258*, 281, 421	
Chromosome Abnormalities.....	79*, 105, 115*,
121*, 125*, 126*, 129, 131*, 133*, 154*, 170*, 174, 175, 177,	
178, 187, 209, 210, 221*, 249, 251*-253*, 255, 256*, 261*, 264,	
265*, 266*, 285*, 287, 374, 386, 397*, 399*, 415*, 421, 424*	
Chromosome Banding.....	1, 14, 16,
22, 35, 42, 61, 79*, 93, 116, 134, 157, 159, 164, 166, 167, 172,	
176, 184, 185, 192, 193, 196, 197, 202, 208, 224, 226, 228, 229,	
248*, 253, 254, 256, 259, 261, 262, 264, 285, 288, 302, 306, 313,	
319, 357, 358, 374, 386, 421, 422	
Chromosome Mapping.....	15*, 19*, 28,
38, 39, 44, 47, 53-56, 61, 63, 65-67, 68*, 74, 75*, 85*, 87, 88, 89*,	
90, 91, 94, 97, 102, 116, 120, 121, 128, 131, 132, 135*, 137, 149,	
151, 153, 154, 156, 163, 168, 169, 172, 175, 178, 179, 186, 187,	
189*, 191, 192, 194, 195, 205, 206, 207*-210*, 212, 213, 216,	
226*, 227, 230*, 231, 232, 235, 236, 237*, 238, 239, 241*, 246,	
247, 251, 256, 257, 289, 300, 304, 312, 313, 328, 357*, 374, 375,	
381, 386, 397, 399, 400, 402, 406, 412	
Chromosomes.....	1*, 3, 4*,

KEYWORDS

ABSTRACT NUMBERS

5, 6, 13, 14*-16*, 19, 20*, 23, 24, 25*, 28*, 30*, 31*, 35*, 38*,	
39, 40*, 41, 42*, 43, 45, 50, 52, 53, 54*-57*, 83, 91, 93*, 94*, 97,	
98*, 102, 104, 107, 109, 111, 116, 117, 119, 120, 123, 125, 126*,	
128, 129, 133, 134, 137, 138*, 140*, 141*, 142, 143, 146*, 147*,	
148*, 149*, 151*-156*, 158*, 159, 160*, 161*, 162, 164*, 167*,	
171*, 172, 174, 176*, 177, 178, 181*-186*, 188*, 189, 190*, 191*,	
193*-197*, 202*, 205*, 206*, 207, 209-211, 212*-221*, 223*-	
232*, 234*-241*, 244, 246, 247*, 249*, 251, 254, 255, 257*, 258,	
261, 264*, 266, 278, 279, 281, 287, 288, 289*, 298, 302*, 306,	
313, 328*, 330*, 346, 347*, 352, 357, 360, 366*-368*, 374*, 380-	
382, 384, 394*, 403, 404, 407, 413, 422	
Chromosomes, Human.....	1*, 3, 4*,
5, 6, 13, 14*-16*, 19, 20*, 23, 24, 25*, 28*, 31*, 35*, 38*, 39,	
40*, 41, 42*, 43, 45, 50, 52, 53, 54*-57*, 91, 93*, 94*, 97, 98*,	
102, 104, 107, 109, 111, 116, 117, 119, 120, 123, 125, 126*,	
129, 133, 134, 137, 140*, 141*, 142, 143, 146*-149*, 151*-	
156*, 158*, 159, 160*, 161*, 162, 164*, 167*-171*, 172, 174,	
176*, 177, 178, 181*-186*, 188*, 189, 190*, 191*, 193*-197*,	
202*, 205*, 206*, 207, 209-211, 212*, 213*, 214*-221*, 223*-	
232*, 234*-241*, 244, 246, 247*, 249*, 251, 254, 255, 257*,	
258, 261, 264*, 266, 278, 279, 281, 288, 289*, 298, 302*, 306,	
313, 328*, 330*, 347*, 357, 360, 366*-368*, 374*, 380-382,	
403, 407, 413, 422	
Chromosomes, Human, 1-3.....	1, 14*-16*, 19,
25*, 28, 93*, 111, 120, 125, 129, 133, 164*, 189, 190*, 191*,	
193*, 229*, 239*, 247*, 255, 278, 313, 328*, 330*, 357, 381,	
382	
Chromosomes, Human, 13-15.....	1, 3, 4*,
5, 19, 20*, 38*, 39, 40*, 41, 45, 50, 57*, 91, 94*, 97, 98*,	
102, 107, 109, 111, 117, 119, 120, 123, 125, 129, 133, 181*,	
206*, 207, 210, 215*-221*, 223*-225*, 227, 238*, 240*,	
241*, 244, 246, 255, 258, 261, 266, 374, 380	
Chromosomes, Human, 16-18.....	23, 111, 123,
125, 133, 188, 214*-217*, 224*, 226*-228*, 232*, 235*-238*,	
240*, 244, 254, 266, 288, 360	
Chromosomes, Human, 19-20.....	50, 164*, 229*-231*,
239*	
Chromosomes, Human, 21-22.....	1, 19, 24,
28, 42*, 43, 111, 116, 120, 123, 126, 133, 134, 137, 140*,	
145, 146*-149*, 151*, 153*-155*, 158*, 159, 160*, 161*,	
162, 164*, 167*-171*, 176*, 177, 178, 181*-186*, 188*,	
195*, 196*, 211, 212*, 244, 246, 251, 261, 266, 298, 407,	
413, 422	
Chromosomes, Human, 4-5.....	156, 234*, 281,
288	
Chromosomes, Human, 6-12.....	1*, 3, 4*,
5, 13, 14*, 16*, 19, 20*, 23, 24, 25*, 28*, 31*, 35*, 38*, 39,	
40*, 41, 42*, 43, 50, 52, 53, 54*-56*, 91, 93*, 97, 98*, 102,	
104, 107, 109, 111, 117, 119, 120, 123, 125, 129, 133, 137,	
140, 141*, 142, 147, 149, 151*, 152*, 154, 156*, 158*, 160*,	
162, 168*, 169*, 171*, 172, 174, 176, 177, 184*, 186*, 189,	
190*, 193*-195*, 196, 197*, 202*, 206*, 209-211, 212*,	
213*, 218*, 219*, 223*, 241*, 246, 266, 288, 289*, 302*,	
306, 357, 366*-368*, 374*, 381	
Nucleolus Organizer Region.....	138*
Sex Chromosomes.....	249, 254, 306
Chronic Disease.....	243
Ciliata.....	384
Clone Cells.....	37, 51, 85,
87*, 110, 146, 185, 199*, 301, 347, 368, 386, 396	
Hela Cells.....	146, 301
Hybridomas.....	87*, 199*
Cloning, Molecular.....	4, 7, 33,
36*, 37, 44*, 46, 62, 63, 71-73, 86*, 99, 101, 104*, 148, 150*,	
159, 161, 169, 189, 192, 193, 197, 203, 204, 214, 216*, 217, 224*,	
225*, 233, 235, 239, 271, 321, 329*, 334, 339, 340, 343, 346*,	
361, 367, 369, 375, 383, 393, 402	
Cocarcinogenesis.....	127*, 393*
Codon.....	48
Colchicine.....	249

KEYWORDS	ABSTRACT NUMBERS
Collodion.....	344
Colonic Diseases.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Colonic Neoplasms.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Colony-Forming Units Assay.....	276, 299*
Communications Media.....	177, 257
Computers.....	323
Connective Tissue Cells.....	17, 23, 76, 101, 142, 188, 192, 201, 226, 234, 236, 284, 327, 341*, 342, 347, 373
Fibroblasts.....	17, 23, 76, 101, 142, 188, 192, 201, 226, 236, 284, 327, 341*, 342, 347, 373
L Cells.....	76, 192
Macrophages.....	234
Contractile Proteins.....	389
Corn.....	404
Cricetidae.....	38, 56, 67, 93, 159, 170, 180, 186, 192, 196, 211, 224, 230, 231, 234, 241, 354, 377, 389, 392, 394
Hamsters.....	38, 56, 67, 93, 159, 170, 180, 186, 192, 196, 211, 224, 230, 231, 234, 241, 354, 377, 389, 392, 394
Cricetulus.....	56, 93, 159, 170, 186, 192, 196, 211, 224, 230, 231, 354, 377, 392, 394
Mesocricetus.....	180
Crosses, Genetic.....	79, 101
Crossing Over (Genetics).....	102, 357*, 388, 393*
Croton Oil.....	275
Cryoprotective Agents.....	275
Culture Media.....	470
Cytogenetics.....	1*, 2, 3, 4*-6*, 7, 8, 9*, 12, 13*-20*, 22*, 23, 24, 25*, 26, 27*, 28, 29*, 31*, 32, 33, 34*, 35*, 37*-39*, 40, 41, 42*, 44*, 45, 46*, 47*, 48, 49*, 50, 51*-57*, 58, 59, 60*-63*, 64, 65*-69*, 70, 71*-79*, 80-82, 83*-85*, 87*-89*, 91, 92, 93*, 94-97, 98*, 102*, 103*, 106, 107*, 108-110, 111*-113*, 114, 115*-120*, 122, 123*, 124, 125, 126*, 127*, 128, 129*, 131*-133*, 134, 135*, 136, 137*, 138*, 139, 140, 141*, 142*, 144, 145, 147*, 148, 149*, 151*-153*, 154-156, 157*-162*, 164*, 167-170, 171*, 172*, 173, 174*, 175-177, 179*, 181*, 182, 183*-186*, 188, 190, 192, 195*, 196*, 197, 202, 203, 205, 206*, 207, 208, 211*, 213, 214*-220*, 221, 222*, 223, 224*, 225*, 226-228, 229*, 230, 234*, 235, 238*, 239, 240*, 242*-244*, 245, 246*-248*, 249, 250-253, 254*, 255*, 256, 257, 258*, 259*, 260, 261, 262*, 263*, 264-266, 270, 274, 281*, 285, 288, 292*, 306*, 312, 328, 336, 341, 347, 357*, 360, 364, 365, 366*, 367, 368*, 371, 374, 380*-382*, 385, 386, 388, 393*, 396-402, 404-406, 407*, 409, 410, 411*, 412-421, 422*, 424*
Cell Cycle.....	12, 15, 54, 61, 73, 108*, 167, 179, 182, 183, 185, 197, 205, 213, 239, 260, 270, 274, 285, 341, 347, 364, 365, 368, 386, 393, 400, 409, 411*, 418
Cell Division.....	12, 15, 54, 61, 73, 108*, 167, 179, 182, 183, 185, 197, 205, 213, 239, 260, 270, 274, 285, 341, 347, 364, 365, 368, 386, 393, 409, 411*, 418
Cell Division Phases.....	15, 54, 61, 167, 182, 185, 197, 205, 213, 239, 285, 347
Metaphase.....	15, 54, 61, 167, 182, 183, 197, 205, 213, 239, 285, 347
Meiosis.....	54
Mitosis.....	260, 386
Chromosome Aberrations.....	1*, 2, 3, 4*-6*, 7, 8, 9*, 13*-20*, 22*, 23, 24, 25*, 26, 27*, 28, 29*-31*, 32, 33, 34*, 35*, 37*-39*, 40, 41, 42*, 44*, 45, 46*, 47*, 48, 49*, 50, 51*, 52*, 53*, 54*-57*, 58, 59, 60*-63*, 64, 65*-69*, 70, 71*-79*, 80, 81, 82, 83*-85*, 87*-89*, 91, 92, 93*, 94-97,

KEYWORDS	ABSTRACT NUMBERS
98*, 102*, 103*, 106, 107*, 108-110, 111*, 112*, 113*, 114, 115*-117*, 118*, 119*, 120*, 122, 123*, 124, 125, 126*, 127*, 128, 129*, 131*-133*, 134*, 135*, 136*, 137*, 138*, 139, 140, 141*, 142*, 144, 145, 147*, 148, 149*, 151*-153*, 154-156, 157*-162*, 164*, 168-170, 171*, 172*, 173, 174*, 175-177, 179*, 181*, 182, 183*-186*, 188, 190, 192, 195*, 196*, 197, 202, 203, 205, 206*, 207, 208, 211*, 214*-219*, 220*, 221, 222*, 223, 224*, 225*, 226-228, 229*, 230, 234*, 235, 238*, 239, 240*, 242*, 243*, 244*, 245, 246*, 247*, 248*, 249, 250, 251-253, 254*, 255*, 256, 257, 258*, 259*, 260, 261, 262*, 263*, 264-266, 281*, 288, 292*, 306*, 312, 328, 336, 360, 366*, 367, 368*, 371, 374, 380*-382*, 385, 386, 393, 396-402, 404, 405, 406, 407*, 409, 410-413, 414, 415, 416, 417, 418, 419-421, 422*, 424*	
Aneuploidy.....	380
Chromosome Deletion.....	62, 110, 155, 190, 203, 234*, 242, 251, 258, 261, 265, 380, 396, 397, 401, 415
Chromosome Fragile Sites.....	157, 179, 248, 253, 254*, 255*, 264, 312, 397
Inversion (Genetics).....	61
Translocation (Genetics).....	1*, 2, 3, 4*-6*, 7, 8, 9*, 13*-20*, 22*, 23, 24, 25*, 26, 27*, 28, 29*-31*, 32, 33, 34*, 35*, 37*-39*, 40, 41, 42*, 44*, 45, 46*, 47*, 48, 49*, 50, 51*, 52*, 53, 54*-57*, 58, 59, 60*-63*, 64, 65*-69*, 70, 71*-79*, 80-82, 83*-85*, 87*-89*, 91, 92, 93*, 94-97, 98*, 102*, 103*, 106, 107*, 108-110, 111*-113*, 114, 116, 117*-120*, 122, 123*, 124, 125, 126*, 127*, 128, 129*, 131*-133*, 134, 135*, 136, 137*, 138*, 139, 140, 141*, 142*, 144, 145, 147*, 148, 149*, 151*-153*, 154-156, 157*-162*, 164*, 168-170, 171*, 172*, 173, 174*, 175-177, 181*, 182, 183*-186*, 188, 192, 195*, 196*, 197, 202, 206*, 207, 208, 211*, 214*-219*, 221-223, 224*, 225*, 226-228, 229*, 230, 235, 238*, 239, 240*, 242, 243, 244*, 245, 246*, 247, 249, 251-253, 255*, 256, 258*, 261, 263-266, 288, 292*, 306*, 328, 366*, 367, 368*, 371, 374, 380, 385, 386, 396-402, 405-407, 409-413, 415-417, 41*-422, 424*
Philadelphia Chromosome.....	137*, 139, 141*, 142, 148, 149*, 152*, 157*, 172*, 174*, 242, 246, 253
Trisomy.....	37, 129, 136, 258*, 281, 421
Crossing Over (Genetics).....	102, 357*, 388, 393*
Mosaicism.....	145, 149*
Ploidies.....	242, 260, 422
Cytological Techniques.....	1, 14, 16, 22, 35, 42, 54, 61, 79*, 93, 101, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 201, 202, 208, 221, 224, 226, 228, 229, 248*, 253, 254, 256, 259-262, 264, 276, 285, 288, 299*, 302, 306, 313, 319, 347, 357, 358, 374, 386, 421, 422
Autoradiography.....	54, 193, 201
Cell Fusion.....	101, 260, 347
Chromosome Banding.....	1, 14, 16, 22, 35, 42, 61, 79*, 93, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 202, 208, 224, 226, 228, 229, 248*, 253, 254, 256, 259, 261, 262, 264, 285, 288, 302, 306, 313, 319, 357, 358, 374, 386, 421, 422
Colony-Forming Units Assay.....	276, 299*
Histocytochemistry.....	221
Cytoplasm.....	64
Cytoskeletal Proteins.....	389
DNA.....	3, 5, 8, 13, 20, 26*, 29, 37, 39*, 41*, 44, 55, 56, 57*, 59*, 63, 69, 77, 81*, 83, 84, 85, 86*, 89*, 90*, 97, 99, 104*, 113, 117, 123, 124, 136, 138, 140, 141, 148, 150, 151, 152, 153, 159, 161, 165, 170, 176, 181, 189, 194, 198*, 201, 204*, 207, 209, 215, 217, 224, 225, 228, 233*, 236, 237, 250, 252*, 257*, 267, 269, 271*, 273, 274, 275, 278*, 281, 285-287, 290, 293, 294, 296, 298*, 303, 307*, 308*, 309-312, 313*, 315, 321, 326, 329, 330*, 332, 335, 336, 339, 341, 343*, 345, 346*, 351*, 354*, 356, 359, 360, 361*, 363-

KEYWORDS

ABSTRACT NUMBERS

366, 367*, 370, 371, 372*, 374, 377, 378, 379*, 383, 384, 386, 388*, 389, 390, 398, 401, 403, 404, 410, 411, 413, 414, 416, 417, 420, 422*	
DNA, Bacterial.....	404
DNA, Neoplasm.....	5, 8, 20, 26*, 39*, 41, 55, 56, 57*, 59*, 69, 81*, 84, 85, 89*, 90*, 97, 99, 124, 138, 141, 150, 153, 161, 165, 170, 194, 201, 204*, 215, 225, 233*, 257*, 267, 269, 271*, 273, 274, 281, 285-287, 294, 298*, 303, 307*, 308*, 309-312, 315, 321, 326, 329, 330*, 332, 335, 336, 343*, 345, 346*, 351*, 354*, 356, 361*, 363, 366, 367*, 370, 374, 378, 379*, 389, 398, 403, 410, 411, 413, 420, 422*
DNA, Recombinant.....	44, 56, 86*, 123, 138, 152, 176, 201, 217, 224, 225, 252*, 377, 384, 414, 417
DNA, Viral.....	99, 201, 296, 359, 404, 413, 416, 417
DNA Insertion Elements.....	62, 193, 203, 250, 258, 408
DNA Repair.....	179
DNA Replication.....	100*, 384, 386, 388, 400
DNA Restriction Enzymes.....	8, 10, 13, 25, 26, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 278, 280, 284, 290, 323, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383
DNA Virus Infections.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Herpesvirus Infections.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Burkitt's Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Infectious Mononucleosis.....	52
DNA Viruses.....	12, 32, 43, 51, 101, 110, 132, 136, 166, 236, 349, 396, 416
DNA Tumor Viruses.....	12, 32, 43, 51, 101, 110, 132, 136, 166, 236, 349, 396, 416
Epstein-Barr Virus.....	12, 32, 43, 51, 110, 132, 166, 396, 416
Papovaviridae.....	101, 236, 349
Herpesviridae.....	12, 32, 43, 51, 110, 132, 166, 396, 416
DNA, Bacterial.....	404
DNA, Neoplasm.....	5, 8, 20, 26*, 39*, 41, 55, 56, 57*, 59*, 69, 81*, 84, 85, 89*, 90*, 97, 99, 124, 138, 141, 150, 153, 161, 165, 170, 194, 201, 204*, 215, 225, 233*, 257*, 267, 269, 271*, 273, 274, 281, 285-287, 294, 298*, 303, 307*, 308*, 309-312, 315, 321, 326, 329, 330*, 332, 335, 336, 343*, 345, 346*, 351*, 354*, 356, 361*, 363, 366, 367*, 370, 374, 378, 379*, 389, 398, 403, 410, 411, 413, 420, 422*
DNA, Recombinant.....	44, 56, 86*, 123, 138, 152, 176, 201, 217, 224, 225, 252*, 377, 384, 414, 417
DNA, Viral.....	99, 201, 296, 359, 404, 413, 416, 417
Dactinomycin.....	270
Demography.....	125, 174, 320
Deoxyribonuclease I.....	8, 10, 27,

KEYWORDS

ABSTRACT NUMBERS

60, 267, 284	
Deoxyribonucleases.....	9
Deoxyribonucleotides.....	332
Dermatologic Agents.....	275, 317*, 318*
Diagnosis, Laboratory.....	143
Digestive System Neoplasms.....	180, 260, 282*, 283*, 285*, 286*, 289, 290*, 291*, 294*, 306*, 310, 331*, 339*, 343*, 353*, 357*, 358*, 359, 376*, 386, 389, 416
Gastrointestinal Neoplasms.....	180, 282*, 283*, 285*, 286*, 289, 294*, 306*, 310, 331*, 343*, 353*, 357*, 358*, 359, 376*, 386, 389, 416
Intestinal Neoplasms.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Colonic Neoplasms.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Stomach Neoplasms.....	180, 282*, 283*, 294*, 331*, 333*, 359, 376*
Liver Neoplasms.....	260, 290*, 291*
Pancreatic Neoplasms.....	339*
Dimethyl Sulfoxide.....	275
Dimethylhydrazines.....	286
Dimethylnitrosamine.....	180*
Diptera.....	384, 389
Disease.....	79, 126, 127, 234, 242, 243, 297
Disease Models, Animal.....	297
Disease Susceptibility.....	79, 127
Diterpenes.....	275, 317*, 318*
Dosage Compensation (Genetics).....	422
Dose-Response Relationship, Drug.....	299
Dose-Response Relationship, Radiation.....	299
Down's Syndrome.....	422
Drosophila.....	384, 389
Drosophila Melanogaster.....	389
Drug Resistance.....	357*, 389, 390, 394
Drug Stability.....	2
Dyes.....	180, 248
Echinodermata.....	249
Electrochemistry.....	47, 52, 57, 143, 162, 201, 282, 290, 295, 337, 344, 351, 366, 376, 378
Electrophoresis.....	47, 52, 57, 143, 162, 201, 282, 290, 295, 337, 344, 351, 366, 376, 378
Electrophoresis, Agar Gel.....	52, 162, 201, 282, 290, 295, 337, 351, 366, 376, 378
Electrophoresis, Polyacrylamide Gel.....	47, 57, 344
Immunoelectrophoresis.....	143
Electrolytes.....	319, 399
Elements.....	319
Embryo.....	32, 101, 321, 322*, 377
Endocrine Gland Neoplasms.....	335*, 345*, 346*, 352*
Endocrine Glands.....	54, 93, 196, 322, 354, 377
Enhancer Elements (Genetics).....	4, 7, 27, 62*
Enzymes.....	8-10, 13, 18, 23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 137*, 140, 141, 143*, 144*, 145, 150, 151, 154, 156, 158, 161, 165*, 169, 172-174, 180*, 188, 191*, 192, 194, 196, 198, 203, 224, 233, 237, 238*, 241, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 361*, 363, 365, 366, 371, 373, 377, 378, 383, 387, 389, 393, 394*, 400, 401, 403, 407, 411
Hydrolases.....	8-10, 13, 18, 23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172,

BEST COPY AVAILABLE

S-9

86

KEYWORDS

ABSTRACT NUMBERS

188, 191*, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383, 407	
Esterases	8-10, 13, 18,
23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383, 407	
Carboxylic Ester Hydrolases	407
Phosphatases	8-10, 13, 18,
23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383	
Phosphodiesterases	8-10, 13, 18,
23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383	
DNA Restriction Enzymes	8, 10, 13,
25, 26, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383	
Deoxyribonuclease I	8, 10, 27,
60, 267, 284	
Deoxyribonucleases	9
Endodeoxyribonucleases	26
Endonucleases	18, 23, 65,
70, 72, 7, 284	
Ribonuclease, Pancreatic	333
Glycoside Hydrolases	191*
Isoenzymes	51, 17*, 192
Ligases	389
Multienzyme Complexes	389
Oxidoreductases	174, 377, 387,
389, 393, 394*	
Transferases	137*, 143*, 144*,
145, 156, 165*, 173, 180*, 238*, 241, 361*, 363, 373, 389, 400, 401, 403, 411	
Acyltransferases	180*
Aspartate Carbamoyltransferase	389
Phosphotransferases	137*, 143*, 144*,
145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411	
Phosphotransferases, ATP	137*, 143*, 144*,
145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411	
Protein Kinases	137*, 143*, 144*,
145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411	
Protein-Tyrosine Kinase	156, 363, 400
Epide nologic Methods	125
Epidermal Growth Factor-Urogastrone	364, 365*, 368,
369*, 371, 372	
Epstein-Barr Virus	12, 32, 43,
51, 110, 132, 166, 396, 416	
Erythroblastosis Virus, Avian	212*, 362*, 371
Erythroulasis	174
Erythrocytes	174
Erythroleukemia	100, 138*, 348*
Esterases	8-10, 13, 18,
23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188,	

KEYWORDS

ABSTRACT NUMBERS

194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383, 407	
Carboxylic Ester Hydrolases	407
Phosphatases	8-10, 13, 18,
23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383	
Phosphodiesterases	8-10, 13, 18,
23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383	
DNA Restriction Enzymes	8, 10, 13,
25, 26, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 278, 280, 284, 290, 323, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383	
Deoxyribonuclease I	8, 10, 27,
60, 267, 284	
Deoxyribonucleases	9
Endodeoxyribonucleases	26
Endonucleases	18, 23, 65,
70, 72, 76, 284	
Ribonuclease, Pancreatic	333
Eukaryotic Cell	390*
Evolution	388, 401, 421*
Extrachromosomal Inheritance	101, 163, 188,
197, 205, 346, 352, 377, 384	
Eye Neoplasms	349, 361, 278*,
326, 327*, 380*, 407, 415	
Face	180
Fanconi's Anemia	179
Fatty Acids	173
Feline Fibrosarcoma Virus	241
Feline Leukemia Virus	99*
Fetal Development	322
Fetal Membranes	377
Fibroblasts	17, 23, 76,
191, 142, 199, 192, 201, 226, 236, 284, 327, 341*, 342, 347, 373	
L Cells	76, 192
Fibrosarcoma	347*, 373, 416
Folic Acid Antagonists	387, 389, 394
Food	404
Friend Virus	344
Carcinogenesis	384
Gamma Rays	342
Gamma-Glutamyltransferase	180*
Gastrointestinal Agents	127, 128, 364,
365*, 368, 369*, 371, 372	
Gastrointestinal Diseases	180, 282*, 283*,
285*, 286*, 289, 294*, 306*, 310, 331*, 343*, 353*, 357*, 358*, 359, 376*, 386, 389, 416	
Gastrointestinal Neoplasms	180, 282*, 283*,
285*, 286*, 289, 294*, 306*, 310, 331*, 343*, 353*, 357*, 358*, 359, 376*, 386, 389, 416	
Intestinal Neoplasms	285*, 286*, 289,
306*, 310, 353*, 357*, 358*, 359, 386, 389, 416	
Colonic Neoplasms	285*, 286*, 289,
306*, 310, 353*, 357*, 358*, 359, 386, 389, 416	
Stomach Neoplasms	180, 282*, 283*,
294*, 331*, 343*, 359, 376*	
Intestinal Diseases	285*, 286*, 289,
306*, 310, 353*, 357*, 358*, 359, 366, 389, 416	
Colonic Diseases	285*, 286*, 289,

KEYWORDS

ABSTRACT NUMBERS

306*, 310, 353*, 357*, 358*, 359, 386, 389, 416	
Colonic Neoplasms	285*, 286*, 289,
306*, 310, 353*, 357*, 358*, 359, 386, 389, 416	
Intestinal Neoplasms	285*, 286*, 289,
306*, 310, 353*, 357*, 358*, 359, 386, 389, 416	
Colonic Neoplasms	285*, 296*, 289,
306*, 310, 353*, 357*, 358*, 359, 386, 389, 416	
Stomach Diseases	180, 282*, 283*,
294*, 331*, 343*, 359, 376*	
Gastrointestinal Hormones	364, 365*, 368,
369*, 371, 372	
Gastrointestinal System	376
Gene Expression Regulation	3, 4, 7,
8*, 17*, 21, 24, 26*, 27*, 40, 45, 50, 52*, 58*, 57*, 63, 64*, 66,	
74, 76*, 78, 82*, 87, 88, 95, 96*, 97*, 106*, 108, 110, 111, 114,	
115, 118, 123, 128, 129, 131, 138*, 144, 153, 159, 162, 165, 166*,	
167*, 169, 172, 178, 179, 199-201, 204*, 206, 245, 250, 252,	
260*, 261, 262, 267*, 268, 271*, 272, 273*, 274*, 277*-281*,	
282*, 283, 284*, 285*, 286*, 287*, 288, 289, 290*, 291, 292*,	
294*, 295*, 296*, 297*, 298, 300, 302, 303*, 304*, 309*, 310*,	
313*, 315*, 316*, 317, 318*, 319*, 320*, 322, 324*, 325*, 326*,	
327*, 328, 329*, 330, 331, 332*, 333*, 334, 335*, 336*, 337*,	
338*, 339, 341*, 342*, 343*, 345*, 346*, 349*-352*, 353, 354*,	
356*, 357*, 358*, 359*, 361*, 363, 364*-366*, 367, 368*, 370,	
371*, 372*, 373, 375-377, 378*, 379*, 381, 382*, 383, 384*, 385*,	
386*, 387*-390*, 392*-394*, 396, 399, 400, 402, 403, 405, 406,	
407, 408-411, 413, 415, 417, 419, 422, 423	
Dosage Compensation (Genetics)	422
Gene Amplification	115, 129, 159,
166*, 167*, 169, 250, 260-262, 267*, 268, 271*, 272, 273*,	
277*-282*, 283, 284*-287*, 288-291, 292*-296*, 298, 302,	
303*, 304*, 309*-313*, 315*, 316*, 319*, 320*, 322, 324*,	
327*, 328, 329*, 330, 331, 332*, 333*, 334, 335*-338*, 339,	
341*-343*, 345*, 346*, 349*-352*, 353, 354*, 356*, 357*, 358,	
359*, 361*, 363, 364*-366*, 367, 368*, 370, 371*, 372*, 373,	
375-377, 378*, 379*, 381, 382*, 383, 384*-390*, 392*-394*,	
399, 402, 403, 406, 407, 411, 413, 416, 419, 422	
Genes, Regulator	4, 7, 8*,
26*, 27*, 40, 45, 62*, 64, 66, 76*, 96*, 405, 411	
Enhancer Elements (Genetics)	4, 7, 27,
62*	
Promoter Regions (Genetics)	64, 66, 76*
RNA Processing, Post-Transcriptional	64*
Gene Frequency	340*
Genes	1, 2*-14*, 15,
17*-21*, 22*, 23*-37*, 38, 39*-42*, 43, 44*, 45, 46*, 48*-56*, 57,	
58*-68*, 70*-74*, 75, 76*-78*, 79, 80*-99*, 100, 101*-105*, 106,	
107, 108*, 109, 110*-112*, 113*, 114*, 115*, 116-118, 119*, 120,	
122*, 123, 124*, 126, 127*, 128*, 130*-132*, 135*, 136,	
137, 138*, 139*, 140, 141*-144*, 145, 146*-151*, 152*, 153*, 154, 155,	
156*, 157, 158*, 159*, 162*, 163*, 164, 165*-169*, 171*, 172, 173*,	
175*, 177, 178*, 179, 181*-183*, 186*, 187*, 189*, 191*, 192*,	
193, 194*, 195*, 196, 197*, 198, 199*-205*, 206, 207*, 208, 209,	
211*-214*, 216-218, 223, 226*-228*, 231*-234*, 238*-241*, 242,	
243*-245*, 246-248, 250, 251, 253, 255-259, 260*, 261, 264,	
265*, 267*-269*, 271*-275*, 277*, 279*-298*, 299, 300*-307*,	
308*, 309*-312*, 313, 314*-341*, 343*, 344, 345*, 346*, 348*-	
353*, 354*, 355*-363*, 366, 369*, 370, 371, 372*-374*, 375*,	
376*-378*, 379, 380, 381*, 382, 383*, 385*, 386*, 387, 388, 393,	
396*, 398*-403*, 404*, 405*, 406*, 408*, 409, 410*-413*, 414*,	
415*-420*, 422, 423*, 424*	
Alleles	8, 10*, 23,
26, 27, 62, 71, 217, 269, 331, 333*	
DNA Insertion Elements	62, 193, 203,
250, 258, 408	
Genes, Dominant	413
Genes, Recessive	413
Genes, Regulator	4, 7, 8*,
26*, 27*, 40, 45, 62*, 64, 66, 76*, 96*, 405, 411	
Enhancer Elements (Genetics)	4, 7, 27,

KEYWORDS

ABSTRACT NUMBERS

62*	
Promoter Regions (Genetics)	64, 66, 76*
Genes, Structural	14*, 17, 18,
24, 33, 35*, 37*, 40, 48, 50, 61*, 67, 68*, 71*, 74, 78, 82, 86*,	
100, 107, 118, 131, 191, 206, 218, 238*, 240*, 289, 305, 360*,	
366, 369*, 370, 372*, 377*, 405	
Genes, Viral	21*, 38, 54*-56*,
99*, 101, 123, 127*, 136, 138, 163, 200*, 203*, 205*, 241*,	
250, 297*, 307*, 308, 349*, 351, 362*, 371, 375*, 377*, 383,	
393, 398, 401, 408, 412-414, 417, 419*, 420*, 423	
Nucleolus Organizer Region	138*
Oncogenes	1, 2*-14*, 15,
17*-21*, 22, 23*-37*, 38, 39*-42*, 43, 44*, 46*, 48*-56*, 58*,	
59*, 60*-68*, 70*-74*, 75, 76*-78*, 79, 80*-95*, 97*-99*, 100,	
101*-105*, 106, 107, 108*, 109, 110*-115*, 116-118, 119*, 120,	
122*, 123, 124*, 126, 127*, 128*, 130*-132*, 135*, 137, 138*,	
139*, 140, 141*-144*, 145, 146*-151*, 152*, 153*, 154, 155,	
156*, 157, 158*, 159*, 162*, 163*, 164, 165*-169*, 171*, 172,	
173*-175*, 177, 178*, 179, 181*-183*, 186*, 187*, 189*, 191*,	
192*, 194*, 195*, 196, 197*, 198, 199*-205*, 206, 208, 211*,	
214*, 216, 223, 226*-228*, 231*, 232*-234*, 239*, 240*, 242,	
243*-245*, 246-248, 250, 251, 253, 255-257, 259, 260*, 261,	
264, 265, 267*, 268*, 269*, 271*-275*, 277*, 279*-298*, 299,	
300*-306*, 309*, 310*-312*, 313, 314*-329*, 330*, 331*-341*,	
343*, 344, 345*, 346*, 348*-353*, 355*-358*, 359*, 360*-363*,	
371, 373*-375*, 376*, 377*, 378*, 379, 380, 381*, 382, 383*,	
385*, 386*, 387, 388, 396*, 398*, 399*, 400*-403*, 404, 405*,	
406*, 408*, 409, 410*-413*, 415*-420*, 422, 423*	
Proto-Oncogenes	59*, 137, 138*,
152*, 156*, 197*, 212*, 231*, 268*, 269*, 309*, 330*, 359*,	
363*, 376*, 399*, 400*	
Operon	23-25, 50, 65*,
70, 80, 82, 129, 292	
Genetic Code	89, 90
Genetic Complementation Test	101
Genetic Marker	137, 138, 226,
242, 247, 248, 251, 259, 306*, 357, 421	
Genetic Techniques	1, 4, 7,
14, 15*, 16, 19*, 22, 28, 33, 35, 36*, 37-39, 42, 44*, 46, 47, 53,	
57, 61-63, 65-67, 68*, 69, 71-75, 79*, 85*, 86*, 87, 88, 89*, 90,	
91, 93, 94, 97-99, 101, 102, 104*, 115, 116, 120, 121, 125, 128,	
129, 131, 132, 134, 135*, 137, 147-149, 150*, 151, 153, 154, 156,	
157, 159, 161, 163, 164, 166*, 167*, 168, 169, 172, 175, 176, 178,	
179, 181, 184-187, 189*, 190-197, 202-206, 207*-210*, 212-214,	
216*, 217, 218, 221, 223, 224*-226*, 227-229, 230*, 231-233,	
235, 236, 237*, 238-240, 241*, 242, 246, 247, 248*, 249-254, 256,	
257, 259-262, 264, 267*, 268, 271*, 272, 273*, 277*-282*, 283,	
284*-287*, 288-291, 292*-296*, 298, 300, 302, 303*, 304*, 306,	
309*-313*, 315*, 316*, 319*, 320*, 321, 322, 324*-327*, 328,	
329*, 330, 331, 332*, 333*, 334, 335*-338*, 339, 340, 341*-343*,	
345*, 346*, 347, 349*-352*, 355, 354*, 356*, 357*, 358, 359*,	
361*, 363, 364*-366*, 367, 368*, 369, 370, 371*, 372*, 373-377,	
377*, 379*, 381, 382*, 383, 384*-390*, 392*-394*, 397, 399, 400,	
402, 403, 406, 407, 411-413, 416, 419, 421*, 422	
Chromosome Banding	1, 14, 16,
22, 35, 42, 61, 79*, 93, 116, 134, 157, 159, 164, 166, 167, 172,	
176, 184, 185, 192, 193, 196, 197, 202, 208, 224, 226, 228, 229,	
248*, 252, 254, 256, 259, 261, 262, 264, 285, 288, 302, 506,	
313, 319, 357, 358, 374, 386, 421, 422	
Chromosome Mapping	15*, 19*, 28,
38, 39, 44, 47, 53-56, 61, 63, 65-67, 68*, 74, 75, 85*, 87, 88,	
89*, 90, 91, 94, 97, 102, 116, 120, 121, 128, 131, 132, 135*,	
137, 145, 151, 153, 154, 156, 163, 165, 169, 172, 175, 178, 179,	
186, 187, 189*, 191, 192, 195, 195, 205, 206, 207*-210*, 212,	
213, 216, 226*, 227, 230*, 231, 232, 235, 236, 237*, 238, 239,	
241*, 246, 247, 251, 256, 257, 289, 300, 504, 312, 313, 324,	
357*, 374, 375, 381, 386, 397, 399, 400, 402, 406, 412	
Cloning, Molecular	4, 7, 33,
36*, 37, 44*, 46, 62, 63, 71-73, 86*, 99, 101, 104*, 148, 150*,	
159, 161, 169, 189, 192, 193, 197, 203, 204, 214, 216*, 217,	

KEYWORDS

ABSTRACT NUMBERS

224*, 225*, 233, 235, 239, 271, 321, 329*, 334, 339, 340, 343, 346*, 361, 367, 369, 375, 383, 393, 402	
Crosses, Genetic	79, 101
Karyotyping	16, 35, 37, 39, 42, 47, 57, 61, 68, 69, 79, 93, 94, 98, 115, 116, 125, 134, 147, 157, 164, 166, 167, 172, 175, 176, 181, 184, 185, 190, 192, 197, 205, 213, 218, 221, 223, 224, 226, 228, 240, 242, 248, 249, 253, 254, 259, 261, 262, 271, 278, 281, 282, 285, 288, 302, 306, 319, 327, 328, 336, 347, 352, 356-358, 367, 378, 386, 399, 421*, 422
Pedigree	181, 252
Genetic Vectors	321, 404
Genetics, Biochemical	2-7, 8*, 9, 10*, 12, 13, 14*, 17*, 18*, 20, 21, 23-25, 26*, 27*, 29-31, 33, 34, 35*, 37*, 39*, 40, 41*, 42*, 44*, 45*, 46, 48, 49*, 50, 52*, 58*, 60*-64*, 65-67, 68*, 70, 71*, 72, 73*, 74, 76*, 77, 78, 80, 81, 82*, 83, 84*, 85, 86*, 87-91, 95, 96*, 97*, 98, 99, 100*, 101, 103*, 104*, 105, 106*, 107, 108, 110, 111, 113-115, 118, 122, 123, 128-132, 138*, 139, 142, 144, 146*, 148, 150*, 151, 153, 158*, 159, 161, 162*, 165, 166*, 167*, 169, 172, 173, 176-179, 189, 191-194, 196, 197, 199-201, 203, 204*, 206, 212-215, 216*, 217-219, 224*, 225*, 228, 233-235, 238*, 239, 240*, 243, 245, 250, 252, 258, 260*, 261, 262, 267*, 268, 269, 271*, 272, 273*, 275*, 277*-282*, 283, 284*-287*, 288, 289, 290*, 291, 292*-297*, 298, 300, 302, 303*, 304*, 305, 307, 309*-313*, 315*, 316*, 317, 318*-320*, 321-323, 324*-327*, 328, 32*, 330, 331, 332*, 333*, 334, 335*-338*, 339, 340, 341*-343*, 345*, 346*, 348, 349*-352*, 353, 354*-361*, 363, 364*-366*, 367, 368*, 369*, 370, 371*, 372*, 373, 375, 376, 377*-379*, 381, 382*, 383, 384*-390*, 392*-394*, 396, 399-403, 405-411, 413, 416-420, 422, 423
Base Sequence	2, 4, 5, 9, 13, 18, 23, 25-27, 29-31, 33, 34, 36, 39-41, 45, 46, 48, 49, 60, 62-65, 70-74, 76-78, 80, 81, 83-86, 89-91, 95, 96, 98, 99, 103, 104, 113, 122, 131, 132, 148, 150, 151, 158, 159, 161, 173, 193, 194, 196, 200, 201, 203, 212, 213, 215, 217, 219, 228, 250, 258, 271, 292, 293, 298, 305, 307, 309, 313, 316, 321, 323, 327, 329, 330, 339, 340, 345, 346, 350, 353, 360, 361, 363, 367, 371, 372, 375, 378, 379, 383, 386, 388, 401, 402, 403, 406, 408, 418, 420
DNA Insertion Elements	62, 193, 203, 250, 258, 408
Repetitive Sequences, Nucleic Acid	71, 200, 316, 353, 383, 401
Sequence Homology, Nucleic Acid	212, 309, 330, 363
Cloning, Molecular	4, 7, 33, 36*, 37, 44*, 46, 62, 63, 71-73, 86*, 99, 101, 104*, 148, 150*, 159, 161, 169, 189, 192, 193, 197, 203, 204, 214, 216*, 217, 224*, 225*, 233, 235, 239, 271, 321, 329*, 334, 339, 340, 343, 346*, 361, 367, 369, 375, 383, 393, 402
DNA Repair	179
DNA Replication	100*, 384, 386, 388, 400
Gene Expression Regulation	3, 4, 7, 8*, 17*, 21, 24, 26*, 27*, 40, 45, 50, 52*, 58*, 62*, 63, 64*, 66, 74, 76*, 78, 82*, 87, 88, 95, 96*, 97*, 106*, 108, 110, 111, 114, 115, 118, 123, 128, 129, 131, 138*, 144, 153, 159, 162, 165, 166*, 167*, 169, 172, 178, 179, 199-201, 204*, 206, 245, 250, 252, 260*, 261, 262, 267*, 268, 271*, 272, 273*, 274*, 277*-281*, 282*, 283, 284*, 285*, 286*, 287*, 288, 289, 290*, 291, 292*-294*, 295*, 296*, 297*, 298, 300, 302, 303*, 304*, 309*, 310*-313*, 315*, 316*, 317, 318*, 319*, 320*, 322, 324*, 325*, 326*, 327*, 328, 329*, 330, 331, 332*, 333*, 334, 335*, 336*, 337*, 338*, 339, 341*, 342*, 343*, 345*, 346*, 349*-352*, 353, 354*, 356*, 357*, 358*, 359*, 361*, 363, 364*-366*, 367, 368*, 370, 371*, 372*, 373, 375-377, 378*, 379*, 381, 382*, 383, 384*, 385*, 386*, 387*-390*, 392*-394*, 396, 399, 400, 402, 403, 405, 406, 407, 408-411, 413, 416, 417, 419, 422, 423
Dosage Compensation (Genetics)	422
Gene Amplification	115, 129, 159,

KEYWORDS

ABSTRACT NUMBERS

166*, 167*, 169, 250, 260-262, 267*, 268, 271*, 272, 273*, 277*-282*, 283, 284*-287*, 288-291, 292*-296*, 298, 302, 303*, 304*, 309*-313*, 315*, 316*, 319*, 320*, 322, 324*-327*, 328, 329*, 330, 331, 332*, 333*, 334, 335*-338*, 339, 341*-343*, 345*, 346*, 349*-352*, 353, 354*, 356*, 357*, 358, 359*, 361*, 363, 364*-366*, 367, 368*, 370, 371*, 372*, 373, 375-377, 378*, 379*, 381, 382*, 383, 384*-390*, 392*-394*, 399, 402, 403, 406, 407, 411, 413, 416, 419, 422	
Genes, Regulator	4, 7, 8*, 26*, 27*, 40, 45, 62*, 64, 66, 76*, 96*, 405, 411
Enhancer Elements (Genetics)	4, 7, 27, 62*
Promoter Regions (Genetics)	64, 66, 76*
RNA Processing, Post-Transcriptional	64*
Genes, Structural	14*, 17, 18, 24, 33, 35*, 37*, 40, 48, 50, 61*, 67, 68*, 71*, 74, 78, 82, 86*, 100, 107, 118, 131, 191, 206, 218, 238*, 240*, 289, 305, 360*, 366, 369*, 370, 372*, 377*, 405
Genetic Code	89, 410
Transcription, Genetic	3, 5-7, 10*, 12, 17, 18*, 20, 21, 27, 29, 37*, 39*, 41*, 42*, 44, 45*, 46, 49*, 50, 60*, 63*, 64*, 73*, 76*, 81, 82, 84*, 85, 89, 95, 96*, 103-105, 108, 113, 123, 130, 139, 142, 146*, 150*, 158*, 162*, 166, 176, 177, 199, 201, 212, 215, 217, 233, 234, 243, 269, 271, 275*, 279, 280, 290, 292*, 295, 296, 333*, 337, 345, 348, 352, 355*, 403, 406, 408, 411
RNA Processing, Post-Transcriptional	64*
Translation, Genetic	103*, 104, 157, 272, 300, 305, 345, 403
Genetics, Microbial	58, 99*, 105, 124, 144, 173, 201, 233, 296, 300, 314, 321, 331, 340, 373, 377, 388, 398, 404, 410, 411, 413, 416, 417
Genetic Vectors	321, 404
Transduction, Genetic	99*, 105, 144, 173, 398, 413
Transfection	58, 105, 124, 201, 233, 296, 300, 314, 321, 331, 340, 373, 377, 388, 410, 411, 416, 417
Genetics, Population	25*, 31, 61*, 92, 160, 181*, 182*, 253, 260*, 269, 292, 311, 340*, 343
Gene Frequency	340*
Hybridization	160, 182*, 311, 343
Polymorphism (Genetics)	181, 253, 269, 340
Variation (Genetics)	25*, 31, 61*, 92, 181*, 260*, 292
Genital Diseases, Female	335*, 349*, 362, 363
Genital Neoplasms, Female	335*, 349*, 362, 363
Genitalia	54, 93, 196, 227, 322, 354, 377
Genitalia, Female	93, 196, 354, 377
Genitalia, Male	54, 322
Genotype	252
Germ Cells	227
Gestational Age	322
Glioblastoma Multiforme	268*, 310, 370*
Glioma	268*, 310, 364*, 370*
Globulins	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127,

KEYWORDS

ABSTRACT NUMBERS

129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 289*, 396, 413	
Serum Globulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Beta Globulins.....	93
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Thyroglobulin.....	289*
Glucosephosphate Dehydrogenase.....	174
Glycoproteins.....	289*
Glycoside Hydrolases.....	191*
Gonads.....	54, 93, 196, 322, 354, 377
Gout Suppressants.....	249
Granulocytes.....	126, 174, 298
Growth Substances.....	108, 139, 183*, 191*, 270, 364, 365*, 368, 369*, 371, 372, 388, 400, 401, 402, 403, 410, 411, 412
Epidermal Growth Factor-Urogastrone.....	364, 365*, 368, 369*, 371, 372
Nerve Growth Factors.....	191*
Platelet-Derived Growth Factor.....	139, 183*, 400, 402, 403, 412
Growth and Embryonic Development.....	5, 10, 12,

KEYWORDS

ABSTRACT NUMBERS

15, 54, 61, 73, 108*, 114, 118, 167, 174, 179, 182, 183, 185, 197, 205, 213, 217, 239, 245, 260, 270, 274, 285, 317, 318, 322, 341, 347, 364, 365, 368, 394, 386, 393, 400, 409, 411*, 418	
Cell Cycle.....	12, 15, 54, 61, 73, 108*, 167, 179, 182, 183, 185, 197, 205, 213, 239, 260, 270, 274, 285, 341, 347, 364, 365, 368, 386, 393, 400, 409, 411*, 418
Cell Division.....	12, 15, 54, 61, 73, 108*, 167, 179, 182, 183, 185, 197, 205, 213, 239, 260, 270, 274, 285, 341, 347, 364, 365, 368, 386, 393, 409, 411*, 418
Cell Division Phases.....	15, 54, 61, 167, 182, 185, 197, 205, 213, 239, 285, 347
Metaphase.....	15, 54, 61, 167, 182, 185, 197, 205, 213, 239, 285, 347
Meiosis.....	54
Mitosis.....	260, 386
Cell Differentiation.....	5, 10, 12, 114, 118, 174, 217, 245, 270, 274, 317, 318, 384, 409
Gestational Age.....	322
Guanine Nucleotide Regulatory Protein.....	400
Guanine Nucleotides.....	400, 403
Guanosine Triphosphate.....	403
Half-Life.....	64, 301
Hamsters.....	38, 56, 67, 93, 159, 170, 180, 186, 192, 196, 211, 224, 230, 231, 234, 241, 354, 377, 389, 392, 394
Cricetulus.....	56, 93, 159, 170, 186, 192, 196, 211, 224, 230, 231, 354, 377, 392, 394
Mesocricetus.....	180
Harvey Sarcoma Virus.....	351, 416
Head.....	180
Health and Disease.....	126, 242, 243
Hela Cells.....	146, 301
Hematologic Diseases.....	30, 52, 57, 100, 116, 121, 126, 129, 133, 134, 138*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 179, 182*, 183*, 186*, 201, 234*, 242, 245, 245*, 246*, 248*, 251, 253, 281, 298*, 302*, 348*, 359, 386, 389, 407, 413, 416, 422
Anemia.....	179, 234*
Blood Protein Disorders.....	30, 57, 201, 248*
Bone Marrow Diseases.....	100, 116, 121, 126, 129, 133, 134, 138*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 234*, 242, 243, 245*, 246*, 251, 253, 298*, 302*, 348*, 359, 386, 389, 407, 413, 416
Anemia, Aplastic.....	179, 234*
Myelodysplastic Syndromes.....	116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 242, 243, 245*, 246*, 251, 253, 298*, 302*, 359, 386, 389, 407, 413, 416
Leukemia, Myelocytic.....	10, 12, 104, 115, 116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 407, 413, 416
Leukemia, Myeloblastic.....	10, 12, 104, 115, 116, 121, 133, 134, 146*, 166*, 174*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 307*, 308*, 310, 318, 356*, 374*
Myeloproliferative Disorder.....	100, 134, 138*, 348*

KEYWORDS	ABSTRACT NUMBERS
Leukocyte Disorders.....	52
Preleukemia.....	281, 422
Hematopoiesis.....	183, 234*
Hematopoietic Stem Cells.....	183, 245*, 270*
Hematopoietic System.....	174, 183, 245*, 270*
Hematoxylin.....	180
Hepatoma.....	290*
Hereditary Diseases.....	252*
Herpesviridae.....	12, 32, 43, 51, 110, 132, 166, 396, 416
Herpesvirus Infections.....	1*-9*, 10, 11*, 12*, 13, 14*, 29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Burkitt's Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Infectious Mononucleosis.....	52
Heterochromatin.....	253
Heterocyclic Cpds, 2-Ring.....	180
Heterocyclic Cpds, 3-Ring.....	248
Histochemistry.....	221
Histological Technics.....	54, 193, 201, 221
History.....	176, 249
History of Medicine.....	176, 249
History of Medicine, 20th Cent.....	176, 249
Hodgkin's Disease.....	253
Homosexuality.....	43
Hormones.....	270, 364, 365*, 368, 369*, 371, 372
Human T-Cell Leukemia Virus.....	220, 243
Hybrid Cells.....	3, 5, 6, 15, 17*, 18, 20, 37, 38, 51, 53, 56, 57, 67, 87*, 114, 117, 118, 137, 142*, 168, 170, 171, 176, 179, 191, 192, 199*, 207, 209, 211, 218, 224, 225, 230, 231, 234, 236, 241, 260*, 347*, 366
Hybridomas.....	87*, 199*
Hybridization.....	160, 182*, 311, 343
Hydrazines.....	286
Hydrocarbons.....	127, 128, 275, 284, 317*, 318*
Hydrogen.....	193, 239
Hydrolases.....	8-10, 13, 18, 23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 191*, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383, 407
Esterases.....	8-10, 13, 18, 23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383, 407
Carboxylic Ester Hydrolases.....	407
Phosphatases.....	8-10, 13, 18, 23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383
Phosphodiesterases.....	8-10, 13, 18,

KEYWORDS	ABSTRACT NUMBERS
23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383	
DNA Restriction Enzymes.....	8, 10, 13, 25, 26, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 278, 280, 284, 290, 323, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383
Deoxyribonuclease I.....	8, 10, 27, 60, 267, 284
Deoxyribonucleases.....	9
Endodeoxyribonucleases.....	26
Endonucleases.....	18, 23, 65, 70, 72, 76, 284
Ribonuclease, Pancreatic.....	333
Glycoside Hydrolases.....	191*
IgA.....	89
IgM.....	34
Immune System.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 78, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 126, 129, 132*, 136, 141, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 234, 243, 248, 251, 253, 270, 289, 297-299, 351, 396, 413, 416
Bone Marrow.....	141, 234, 243, 248, 270, 299
Leukocytes.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 126, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 234, 251, 253, 269, 298, 351, 396, 413, 416
Granulocytes.....	126, 174, 298
Lymphocytes.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 251, 253, 289, 396, 413, 416
B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
T Lymphocytes.....	33*, 79, 92*, 94, 125, 174, 206-208, 215, 221*, 222, 233, 253, 416
Monocytes.....	234
Lymphatic System.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 78, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 251, 253, 289, 297, 299, 396, 413, 416
Antibody-Producing Cells.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
Lymphocytes.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 251, 253, 289, 396, 413, 416

KEYWORDS

ABSTRACT NUMBERS

B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
T Lymphocytes.....	33*, 79, 92*, 94, 125, 174, 206-208, 215, 221*, 222, 233, 253, 416
Lymphoid Tissue.....	78, 122, 297, 299
Phagocytes.....	174, 234
Reticuloendothelial System.....	234
Immunity.....	49, 79, 81, 84, 85, 117, 206*-210*, 255*, 307, 346
Antibody Formation.....	117
Antibody Specificity.....	49, 79, 81, 84, 85, 346
Immunity, Cellular.....	307
Receptors, Immunologic.....	206*-210*, 255*
Immunochemistry.....	344
Immunoelectrophoresis.....	143
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 174, 206*-210*, 215-217, 218*, 219, 222, 223, 255*, 271, 307, 319, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*,

KEYWORDS

ABSTRACT NUMBERS

27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*	
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Immunologic Deficiency Syndromes.....	43, 179, 209, 210, 255*
Immunologic Factors.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 174, 206*-210*, 215-217, 218*, 219, 222, 223, 235*, 236*, 243, 255*, 271, 307, 319, 396, 413, 418
Antibodies.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 174, 207*, 215-217, 218*, 219, 222, 223, 235*, 236*, 243, 255*, 271, 307, 319, 396, 413
Agglutinins.....	307
Antibodies, Monoclonal.....	174, 243, 271, 319
Antibodies, Neoplasms.....	107*, 174
Binding Sites, Antibody.....	48, 86, 215
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 174, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*,

KEYWORDS

ABSTRACT NUMBERS

17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*	
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Antigens.....	43, 174, 223, 235*, 236*, 418
Interferons.....	243
Receptors, Immunologic.....	206*-210*, 255*
Immunologic Technics.....	307
Immunoproliferative Disorders.....	1*-9*, 10, 11*-29*, 30, 31*-36*, 37, 38*-50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*-92*, 94*, 95*, 96, 97*, 98*, 102*, 103*, 104, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*-123*, 124, 125*-129*, 131*-133*, 134, 136, 137*, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*-172*, 173, 174*-177*, 178, 182*, 183*, 186*, 195*, 196*, 197, 198*, 199*, 201, 203*, 204*, 207, 208, 213, 214*-219*, 221*, 222*, 225*, 226*, 228*, 230*, 233*, 235*, 238*, 240*, 242*, 243, 244*-246*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 270*, 271*, 274*, 275*, 280*, 281*, 288*, 296*-298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 396, 398, 405, 407, 408, 413, 414, 416, 420, 422
Lymphoproliferative Disorders.....	1*-9*, 10, 11*-29*, 30, 31*-36*, 37, 38*-50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*-92*, 94*, 95*, 96, 97*, 98*, 102*, 103*, 104, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*-123*, 124, 125*-129*, 131*-133*, 134, 136, 137*, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*-172*, 173, 174*-177*, 178, 182*, 183*, 186*, 195*, 196*, 197, 198*, 199*, 201, 203*, 204*, 207, 208, 213, 214*-219*, 221*, 222*, 225*, 226*, 228*, 230*, 233*, 235*, 238*, 240*, 242*, 243, 244*-246*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 270*, 271*, 274*, 275*, 280*, 281*, 288*, 296*-298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 396, 398, 405, 407, 408, 413, 414, 416, 420, 422
Infectious Mononucleosis.....	52
Leukemia, Hairy Cell.....	243
Leukemia, Lymphocytic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 111, 125*, 133, 134, 137*, 167*, 175, 178, 197, 198, 214, 218*, 219*, 221*, 222*, 225, 230*, 242, 251, 253, 296
Leukemia, Lymphoblastic.....	6*, 13*, 18*,

KEYWORDS

ABSTRACT NUMBERS

51, 91*, 94*, 97*, 98*, 125*, 133, 137*, 167*, 178, 197, 198, 214, 230*, 242, 251, 253, 296	
Leukemia, Monocytic.....	121, 134, 242, 251, 253
Leukemia, Myelocytic.....	10, 12, 104, 115, 116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 407, 413, 416
Leukemia, Myeloblastic.....	10, 12, 104, 115, 116, 121, 133, 134, 146*, 166*, 174*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 307*, 308*, 310, 318, 356*, 374*
Leukemia, Plasmacytic.....	248, 280*
Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33*, 34*, 35*, 36*, 37, 38*, 48*, 49*, 50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*, 67*, 68*, 69*-81*, 83*, 84*, 85*, 86, 87*, 89*, 90*, 92*, 95*, 96, 102*, 103*, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*, 119*, 120*-123*, 124, 125*, 126*, 127*-129*, 131*, 132*, 133*, 136, 175*, 199*, 201, 203*, 204*, 207, 208, 213, 214*, 215*, 216*, 217*, 218, 219*, 221*, 222*, 225*, 233*, 242*, 244*, 245*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 296*, 297*, 374*, 396, 398, 405, 407, 408, 414, 416, 420, 422
Burkitt's Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*, 50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Hodgkin's Disease.....	253
Lymphoma, Giant Follicular.....	121, 215*, 217*
Lymphosarcoma.....	122, 203*, 204*, 374*
Plasmacytoma.....	20, 21*, 30, 31, 33, 37, 41*, 49, 51, 55*, 57, 58*, 59*, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*, 90*, 92, 110, 113, 117, 120, 122, 124, 127*-129*, 132*, 199*, 201, 204, 208, 218, 248*, 258, 396, 398
Multiple Myeloma.....	30, 57, 201, 248*
Paraproteinemia.....	30, 57, 201, 248*
Immunoproteins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*,

KEYWORDS

ABSTRACT NUMBERS

75, 86, 90	
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 61*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 37*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Inclusion Bodies, Viral.....	200*
Infant.....	315, 320, 326, 415
Infant, Newborn.....	415
Infectious Mononucleosis.....	52
Information Services.....	257
Insects.....	384, 389
Interferon Type I.....	243
Interferons.....	243
Intestinal Diseases.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Colonic Diseases.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Colonic Neoplasms.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Intestinal Neoplasms.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Colonic Neoplasms.....	285*, 286*, 289, 306*, 310, 353*, 357*, 358*, 359, 386, 389, 416
Inversion (Genetics).....	61
Iodoproteins.....	289*
Ion Channels.....	319
Ions.....	319, 399
Isoenzymes.....	51, 174, 192
Isotopes.....	193, 239, 301
Karyotyping.....	16, 35, 37, 39, 42, 47, 57, 61, 68, 69, 79, 93, 94, 98, 115, 116, 125, 134, 147, 157, 164, 166, 167, 172, 175, 176, 181, 184, 185, 190, 192, 197, 205, 213, 218, 221, 223, 224, 226, 228, 240, 242, 248, 249, 253, 254, 259, 261, 262, 271, 278, 281, 282, 285, 288, 302, 306, 319, 327, 328, 336, 347, 352, 356-358, 367, 378, 386, 399, 421*, 422
Keratolytic Agents.....	317*, 318*
Kidney.....	59, 81, 322
Kidney Diseases.....	93*, 129
Kidney Neoplasms.....	93*, 129
Kinetics.....	2, 11
Kirsten Sarcoma Virus.....	398, 416
L Cells.....	76, 192
Lagomorpha.....	179
Lectins.....	307
Leukemia.....	6*, 10, 12,

KEYWORDS

ABSTRACT NUMBERS

13*, 18*, 36*, 47*, 51, 88*, 91*, 94*, 95*, 97*, 98*, 99*, 104, 111, 115*, 116*, 121*, 123*, 125*, 125*, 128, 129, 133*, 134*, 136, 137*, 138*, 139*, 140*-143*, 145*, 146*, 147*-152*, 154*, 155*, 156*, 157*, 158*, 159*, 160*, 161*, 162*, 164, 165*-172*, 173*, 174*, 173*, 176*, 177*, 178*, 182*, 183*, 186*, 187*, 195*, 196*, 197, 198*, 206*, 207, 208*, 211*, 214, 215*, 218*, 219*, 220*, 221*, 222*, 223*-225*, 226*, 228*, 230*, 235*, 238*, 240*, 242*-244*, 245*, 246*, 247, 248, 251*, 253*, 256*, 257, 261, 262*, 263*, 264, 266*, 269, 270*, 271*, 274*, 275*, 280*, 281*, 288*, 296*, 297*, 298*, 302*, 307*, 308*, 310, 318, 356*, 359, 363, 374*, 385, 386, 389, 405, 407, 413, 414, 416, 422*	
Leukemia, Experimental.....	47*, 88*, 95*, 128, 136, 138*, 165*, 187*, 297*, 308, 405
Avian Leukosis.....	95*, 297*, 405
Leukemia, Hairy Cell.....	243
Leukemia, Lymphocytic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 111, 125*, 133, 134, 137*, 167*, 175, 178, 197, 198, 214, 218*, 219*, 221*, 222*, 225, 230*, 242, 243, 253, 296
Leukemia, Lymphoblastic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 125*, 133, 134, 137*, 167*, 178, 197, 198, 214, 230*, 242, 251, 253, 296
Leukemia, Monocytic.....	171, 124, 242, 251, 253
Leukemia, Myelocytic.....	10, 12, 104, 115, 116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 407, 413, 416
Leukemia, Myeloblastic.....	10, 12, 104, 115, 116, 121, 133, 134, 146*, 166*, 174*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 307*, 308*, 310, 318, 356*, 374*
Leukemia, Plasmacytic.....	248, 280*
Leukemia, Monoblastic.....	121, 134, 242, 251, 253
Leukocyte Disorders.....	52
Leukocytes.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 126, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 234, 251, 253, 289, 298, 351, 396, 413, 416
Granulocytes.....	126, 174, 298
Lymphocytes.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 251, 253, 289, 396, 413, 416
B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
T Lymphocytes.....	33*, 79, 92*, 94, 125, 174, 206-208, 215, 221*, 222, 233, 253, 416
Monocytes.....	234
Ligases.....	389
Linkage (Genetics).....	100, 191, 200, 226
Lipids.....	173, 275
Liver.....	59, 81
Liver Diseases.....	260, 290*, 291*
Liver Neoplasms.....	260, 290*, 291*
Liver Neoplasms, Experimental.....	291*
Longitudinal Studies.....	125

KEYWORDS	ABSTRACT NUMBERS
Lung.....	192, 276, 29*
Lung Diseases.....	110, 202, 267*, 273*, 276*, 277*, 292*, 299*, 303*, 309*, 310, 330*, 332*, 336*, 350*, 353*, 355*, 385, 396, 416
Lung Neoplasms.....	110, 202, 267*, 273*, 276*, 277*, 292*, 299*, 303*, 309*, 310, 330*, 332*, 336*, 350*, 353*, 355*, 385, 396, 416
Bronchial Neoplasms.....	273*
Lymph Nodes.....	299
Lymphatic Diseases.....	1*-9*, 10, 11*-29*, 30, 31*-36*, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 64, 68, 83, 85*, 91*, 92*, 94*, 95*, 96, 97*, 98*, 102*, 103*, 105, 106*, 109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*-123*, 124, 125*, 126*, 129*, 131*-133*, 134, 136, 137*, 167*, 175*, 178, 197, 198, 203*, 204*, 207, 213, 214*, 216*, 218*, 219*, 221*, 222*, 225*, 230*, 233*, 242*, 243, 244*, 245*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 296*, 297*, 374*, 396, 398, 405, 407, 408, 414, 416, 420, 422
Lymphoproliferative Disorders.....	1*-9*, 10, 11*-29*, 30, 31*-36*, 37, 38*-50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*-92*, 94*, 95*, 96, 97*, 98*, 102*, 103*, 104, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*-123*, 124, 125*-129*, 131*-133*, 134, 136, 137*, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*-172*, 173, 174*-177*, 178, 182*, 183*, 186*, 195*, 196*, 197, 198*, 199*, 201, 203*, 204*, 207, 208, 213, 214*-219*, 221*, 222*, 225*, 226*, 228*, 230*, 233*, 235*, 238*, 240*, 242*, 243, 244*-246*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 270*, 271*, 274*, 275*, 280*, 281*, 288*, 296*-298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 396, 398, 405, 407, 408, 413, 414, 416, 420, 422
Infectious Mononucleosis.....	*2
Leukemia, Hairy Cell.....	243
Leukemia, Lymphocytic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 111, 125*, 133, 134, 137*, 167*, 175, 178, 197, 198, 214, 218*, 219*, 221*, 222*, 225, 230*, 242, 251, 253, 296
Leukemia, Lymphoblastic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 125*, 133, 134, 137*, 167*, 178, 197, 198, 214, 230*, 242, 251, 253, 296
Leukemia, Monocytic.....	121, 134, 242, 251, 253
Leukemia, Myelocytic.....	10, 12, 104, 115, 116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 407, 413, 416
Leukemia, Myeloblastic.....	10, 12, 104, 115, 116, 121, 133, 134, 146*, 166*, 174*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 307*, 308*, 310, 318, 356*, 374*
Leukemia, Plasmacytic.....	248, 280*
Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33*, 34*, 35*, 36*, 37, 38*- 48*, 49*, 50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*- 67*, 68*, 69*-81*, 83*, 84*, 85*, 86, 87*, 89*, 90*, 92*, 95*, 96, 102*, 103*, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*, 119*, 120*-123*, 124, 125*, 126*, 127*-129*, 131*, 132*, 133*, 136, 175*, 199*, 201, 203*, 204*, 207, 208, 213, 214*, 215*, 216*, 217*, 218, 219*, 221*, 222*, 225*, 233*, 242*, 244*, 245*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 296*, 297*, 374*, 396, 398, 405, 407, 408, 414, 416, 420, 422
Burkitt's Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*- 50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*,

KEYWORDS	ABSTRACT NUMBERS
110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420	
Hodgkin's Disease.....	253
Lymphoma, Giant Follicular.....	121, 215*, 217*
Lymphosarcoma.....	122, 203*, 204*, 374*
Plasmacytoma.....	20, 21*, 30, 31, 33, 37, 41*, 49, 51, 55*, 57, 58*, 59*, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*, 90*, 92, 110, 113, 117, 120, 122, 124, 127*-129*, 132*, 199*, 201, 204, 208, 218, 248*, 258, 396, 398
Multiple Myeloma.....	30, 57, 201, 248*
Lymphatic Metastasis.....	272, 294, 326
Lymphatic System.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 78, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 251, 253, 289, 297, 299, 396, 413, 416
Antibody-Producing Cells.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
Lymphocytes.....	5, 12, 18*, 23, 33*, 41, 47*, 51*, 52, 54, 64, 73*, 79, 92*, 94, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 125, 129, 132*, 136, 166, 174, 189, 197, 206-208, 213, 214, 215*, 217, 218*, 219, 221*, 222, 223, 224*, 225, 230, 233, 251, 253, 289, 396, 413, 416
B Lymphocytes.....	18*, 33*, 41, 47*, 51*, 52, 64, 92*, 95, 110, 111*, 112, 114, 118*, 120, 122*, 123*, 129, 132*, 136, 174, 214, 215*, 217, 218*, 219, 223, 224*, 225, 230, 396, 413, 416
T Lymphocytes.....	33*, 79, 92*, 94, 125, 174, 206-208, 215, 221*, 223, 233, 253, 416
Lymphoid Tissue.....	78, 122, 297, 299
Lymphocyte Transformation.....	307
Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33*, 34*, 35*, 36*, 37, 38*-48*, 49*, 50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*-67*, 68*, 69*-81*, 83*, 84*, 85*, 86, 87*, 89*, 90*, 92*, 95*, 96, 102*, 103*, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*, 119*, 120*-123*, 124, 125*, 126*, 127*-129*, 131*, 132*, 133*, 136, 175*, 199*, 201, 203*, 204*, 207, 208, 213, 214*, 215*, 216*, 217*, 218, 219*, 221*, 222*, 225*, 233*, 242*, 244*, 245*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 296*, 297*, 374*, 396, 398, 405, 407, 408, 414, 416, 420, 422
Burkitt's Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 215, 242, 249, 253, 258, 396, 407, 414, 416, 420
Hodgkin's Disease.....	253
Lymphoma, Giant Follicular.....	121, 215*, 217*
Lymphosarcoma.....	122, 203*, 204*, 374*
Plasmacytoma.....	20, 21*, 30, 31, 33, 37, 41*, 49, 51, 55*, 57, 58*, 59*, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*, 90*, 92, 110, 113, 117, 120, 122, 124, 127*-129*, 132*, 199*, 201, 204, 208, 218, 248*, 258, 396, 398

KEYWORDS

ABSTRACT NUMBERS

Multiple Myeloma.....	30, 57, 201, 248*
Lymphoproliferative Disorders.....	1*-9*, 10, 11*-29*, 30, 31*-36*, 37, 38*-50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*-92*, 94*, 95*, 96, 97*, 98*, 102*, 103*, 104, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*-123*, 124, 125*-129*, 131*-133*, 134, 135, 137*, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*-172*, 173, 174*-177*, 178, 182*, 183*, 186*, 195*, 196*, 197, 198*, 199*, 201, 203*, 204*, 207, 208, 213, 214*-219*, 221*, 222*, 225*, 226*, 228*, 230*, 233*, 235*, 238*, 240*, 242*, 243, 244*-246*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 270*, 271*, 274*, 275*, 280*, 281*, 288*, 296*-298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 396, 398, 405, 407, 408, 413, 414, 416, 420, 422
Infectious Mononucleosis.....	52
Leukemia, Hairy Cell.....	243
Leukemia, Lymphocytic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 111, 125*, 133, 134, 137*, 167*, 175, 178, 197, 198, 214, 218*, 219*, 221*, 222*, 225, 230*, 242, 251, 253, 296
Leukemia, Lymphoblastic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 125*, 133, 134, 137*, 167*, 178, 197, 198, 214, 230*, 242, 251, 253, 296
Leukemia, Monocytic.....	121, 134, 242, 251, 253
Leukemia, Myelocytic.....	10, 12, 104, 115, 116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 407, 413, 416
Leukemia, Myeloblastic.....	10, 12, 104, 115, 116, 121, 133, 134, 146*, 166*, 174*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 307*, 308*, 310, 318, 356*, 374*
Leukemia, Plasmacytic.....	248, 280*
Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33*, 34*, 35*, 36*, 37, 38*-48*, 49*, 50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*-67*, 68*, 69*-81*, 83*, 84*, 85*, 86, 87*, 89*, 90*, 92*, 95*, 96, 102*, 103*, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*, 119*, 120*-123*, 124, 125*, 126*, 127*-129*, 131*, 132*, 133*, 136, 175*, 199*, 201, 203*, 204*, 207, 208, 213, 214*, 215*, 216*, 217*, 218, 219*, 221*, 222*, 225*, 233*, 242*, 244*, 245*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 296*, 297*, 374*, 396, 398, 405, 407, 408, 414, 416, 420, 422
Burkitt's Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Hodgkin's Disease.....	253
Lymphoma, Giant Follicular.....	121, 215*, 217*
Lymphosarcoma.....	122, 203*, 204*, 374*
Plasmacytoma.....	20, 21*, 30, 31, 33, 37, 41*, 49, 51, 55*, 57, 58*, 59*, 51*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*, 90*, 92, 110, 113, 117, 120, 122, 124, 127*-129*, 132*, 199*, 201, 204, 208, 218, 248*, 258, 396, 398
Multiple Myeloma.....	30, 57, 201, 248*
Macrophages.....	234
Mammals.....	3, 17, 20, 21, 30-32, 37, 38, 41, 46, 49, 51, 53, 55-90, 92, 93, 99-101, 113, 117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136-138, 142,

KEYWORDS

ABSTRACT NUMBERS

143, 159, 163, 170, 173, 177, 179, 180, 186-188, 192, 196, 197, 199, 201, 203, 204, 207-211, 218, 224, 225, 228, 230, 231, 233, 234, 236, 241, 245, 258, 279, 282, 284, 286, 287, 289, 291, 294, 296, 299, 300, 311, 314, 321, 322, 331, 336, 337, 344-346, 348, 350, 352, 354, 363, 366, 373, 377, 384, 387, 389, 392, 394, 398, 410, 413, 417, 419, 420	
Carnivora.....	99, 354, 417, 419, 420
Lagomorpha.....	179
Primates.....	419
Rodentia.....	3, 17, 20, 21, 30-32, 37, 38, 41, 46, 49, 51, 53, 55-90, 92, 93, 100, 101, 113, 117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136-138, 142, 143, 159, 163, 170, 173, 177, 179, 180, 186-188, 192, 196, 197, 199, 201, 203, 204, 207-211, 218, 224, 225, 228, 230, 231, 233, 234, 236, 241, 245, 258, 279, 282, 284, 286, 287, 289, 291, 294, 296, 299, 300, 311, 314, 321, 322, 331, 336, 337, 344-346, 348, 350, 352, 354, 363, 366, 373, 377, 387, 389, 392, 394, 398, 410, 413, 417, 419
Cricetidae.....	38, 56, 67, 93, 159, 170, 180, 186, 192, 196, 211, 224, 230, 231, 234, 241, 354, 377, 389, 392, 394
Hamsters.....	38, 56, 67, 93, 159, 170, 180, 186, 192, 196, 211, 224, 230, 231, 234, 241, 354, 377, 389, 392, 394
Cricetulus.....	56, 93, 159, 170, 186, 192, 196, 211, 224, 230, 231, 354, 377, 392, 394
Mesocricetus.....	180
Muridae.....	3, 17, 20, 21, 30-32, 37, 38, 41, 46, 49, 51, 53, 55-90, 92, 100, 101, 113, 117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136-138, 142, 143, 159, 163, 173, 177, 179, 186-188, 192, 197, 199, 201, 203, 204, 207-210, 218, 224, 225, 228, 231, 233, 236, 241, 245, 258, 279, 282, 284, 286, 287, 289, 291, 294, 296, 299, 300, 311, 314, 321, 322, 331, 336, 337, 344-346, 348, 350, 352, 354, 363, 366, 373, 377, 387, 389, 392, 394, 398, 410, 413, 417, 419
Mice.....	3, 17, 20, 21, 30, 31, 37, 38, 41, 46, 49, 51, 53, 55-87, 89, 90, 92, 100, 113, 117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136, 137, 142, 143, 159, 163, 173, 177, 179, 186-188, 192, 197, 199, 201, 203, 204, 207-210, 218, 224, 225, 228, 231, 233, 236, 241, 245, 258, 279, 282, 284, 286, 287, 289, 291, 294, 296, 299, 300, 311, 314, 322, 331, 336, 337, 345, 346, 348, 350, 352, 354, 363, 366, 373, 377, 387, 392, 394, 398, 410, 413, 417, 419
Mice, Inbred Strains.....	41, 61, 68, 69, 71, 73, 77, 79, 81, 83, 127, 201, 203, 204, 284, 286, 296, 348, 350, 354
Mice, Inbred AKR.....	61, 68, 79
Mice, Inbred BALB C.....	41, 69, 71, 73, 77, 79, 81, 83, 127, 201, 203, 204, 284, 286, 296
Mice, Mutant Strains.....	279, 282, 299, 311, 314, 336, 350
Rats.....	32, 88, 101, 130, 138, 179, 291, 314, 321, 344, 354, 363, 389, 392, 398, 410, 413, 417, 419
Rats, Inbred Strains.....	21, 344
Mammary Cancer Virus.....	416
Mammary Neoplasms, Experimental.....	344*
Materials.....	127, 128
Mathematics.....	121, 254
Megakaryocytes.....	174
Meiosis.....	54
Melanoma.....	229*, 334*, 398
Membrane Proteins.....	93, 230*, 344, 359, 360*-362*, 363, 364*-372*, 400, 401, 411
Receptors, Endogenous Substances.....	93, 230*, 344,

KEYWORDS	ABSTRACT NUMBERS
359, 360*-362*, 363, 364*-372*, 400, 401, 411	
Guanine Nucleotide Regulatory Protein.....	400
Receptors, Insulin.....	230*
Receptors, Steroid.....	344
Membranes.....	180
Meningeal Neoplasms.....	181*
Meningioma.....	181*
Mental Disorders.....	252, 422
Mental Retardation.....	252, 422
Mesocricetus.....	180
Metabolic Diseases.....	252
Metabolism, Inborn Errors.....	252
Metalloproteins.....	93
Metals.....	319
Metals, Alkali.....	319
Metaphase.....	15, 54, 61,
167, 182, 185, 197, 205, 213, 239, 285, 347	
Methods.....	252
Methotrexate.....	387, 389, 394
Methylation.....	59, 81, 82,
267, 274, 275	
Methylhydrazines.....	286
Mice.....	3, 17, 20,
21, 30, 31, 37, 38, 41, 46, 49, 51, 53, 55-57, 89, 90, 92, 100, 113,	
117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136, 137, 142,	
143, 159, 163, 173, 177, 179, 186-188, 192, 197, 199, 201, 203,	
204, 207-210, 218, 224, 225, 228, 231, 233, 236, 241, 245, 258,	
279, 282, 284, 286, 287, 289, 294, 296, 299, 300, 311, 314, 322,	
331, 336, 337, 345, 346, 348, 350, 352, 354, 363, 366, 373, 377,	
387, 392, 394, 398, 410, 413, 417, 419	
Mice, Inbred Strains.....	41, 61, 68,
69, 71, 73, 77, 79, 81, 83, 127, 201, 203, 204, 284, 286, 296,	
348, 350, 354	
Mice, Inbred AKR.....	61, 68, 79
Mice, Inbred BALB C.....	41, 69, 71,
73, 77, 79, 81, 83, 127, 201, 203, 204, 284, 286, 296	
Mice, Mutant Strains.....	279, 282, 299,
311, 314, 336, 350	
Mice, Nude.....	279, 282, 299,
311, 314, 336, 350	
Microbiologic Phenomena.....	58, 95, 105,
108, 110, 114, 124, 127, 132, 165*, 179, 200*, 201, 233, 236, 284,	
296*, 297, 300, 305*, 314, 321, 331, 340, 371*, 377, 388, 396,	
401, 406, 410, 411, 413, 416, 417, 419, 423	
Cell Transformation, Viral.....	95, 108, 110,
114, 132, 165*, 179, 236, 284, 296*, 297, 305*, 373*, 396, 401,	
406, 413, 416, 419, 423	
Inclusion Bodies, Viral.....	260*
Transfection.....	58, 105, 124,
201, 233, 296, 300, 314, 321, 331, 340, 373, 377, 388, 410, 411,	
416, 417	
Virus Replication.....	127, 419
Microfilament Proteins.....	389
Middle Age.....	125, 137, 140,
141, 148, 149, 152, 157, 162, 181, 190, 220-222, 248, 269, 281,	
283, 326, 335, 349	
Middle East.....	419
Mineral Oil.....	127, 128
Mink.....	354
Mitogens.....	307
Mitosis.....	260, 386
Models, Molecular.....	177
Models, Structural.....	177
Models, Theoretical.....	30, 83, 113,
131, 135, 172*, 177, 245, 383, 384, 393*, 409*, 413	
Models, Biological.....	30, 83, 113,
131, 172*, 177, 245, 383, 384, 393*, 409*, 413	
Models, Genetic.....	30, 83, 113,

KEYWORDS	ABSTRACT NUMBERS
172*, 177, 245, 383, 384, 393*, 409*, 413	
Molecular Conformation.....	198*, 219, 367
Molecular Weight.....	144, 146, 158,
201, 301, 351, 355	
Moloney Sarcoma Virus.....	197*, 375
Monocytes.....	234
Mosaicism.....	145, 149*
Mouse Tumor Viruses.....	54, 122, 127,
128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241,	
284*, 348, 351, 353*, 375, 383, 398, 416	
Mammary Cancer Virus.....	416
Mouse Leukemia Viruses.....	54, 122, 127,
128, 138, 143*, 144, 163, 168, 169*, 173, 203*, 204, 241, 284*,	
348, 383	
Abelson Leukemia Virus.....	122, 127, 128,
138, 143*, 144, 163, 168, 169*, 204, 241, 284*	
Friend Virus.....	348
Moloney Leukemia Virus.....	54, 203*, 383
Mouse Sarcoma Viruses.....	197*, 351, 353*,
375, 398, 416	
Mouth.....	180
Mouth Diseases.....	180*, 363*
Mouth Mucosa.....	180
Mouth Neoplasms.....	180*, 363*
Mucous Membrane.....	180
Multienzyme Complexes.....	389
Multiple Myeloma.....	30, 57, 201,
248*	
Muridae.....	3, 17, 20,
21, 30-32, 37, 38, 41, 46, 49, 51, 53, 55-90, 92, 100, 101, 113,	
117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136-138, 142,	
143, 159, 163, 173, 177, 179, 186-188, 192, 197, 199, 201, 203,	
204, 207-210, 218, 224, 225, 228, 231, 233, 236, 241, 245, 258,	
279, 282, 284, 286, 287, 289, 291, 294, 296, 299, 300, 311, 314,	
321, 322, 331, 336, 337, 344-346, 348, 350, 352, 354, 363, 366,	
373, 377, 387, 389, 392, 394, 398, 410, 413, 417, 419	
Mice.....	3, 17, 20,
21, 30, 31, 37, 38, 41, 46, 49, 51, 53, 55-87, 89, 90, 92, 100,	
113, 117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136,	
137, 142, 143, 159, 163, 173, 177, 179, 186-188, 192, 197, 199,	
201, 203, 204, 207-210, 218, 224, 225, 228, 231, 233, 236, 241,	
245, 258, 279, 282, 284, 286, 287, 289, 294, 296, 299, 300, 311,	
314, 322, 331, 336, 337, 345, 346, 348, 350, 352, 354, 363, 366,	
373, 377, 387, 392, 394, 398, 410, 413, 417, 419	
Mice, Inbred Strains.....	41, 61, 68,
69, 71, 73, 77, 79, 81, 83, 127, 201, 203, 204, 284, 286, 296,	
348, 350, 354	
Mice, Inbred AKR.....	61, 68, 79
Mice, Inbred BALB C.....	41, 69, 71,
73, 77, 79, 81, 83, 127, 201, 203, 204, 284, 286, 296	
Mice, Mutant Strains.....	279, 282, 299,
311, 314, 336, 350	
Rats.....	32, 88, 101,
130, 138, 179, 291, 314, 321, 344, 354, 363, 389, 392, 398, 410,	
413, 417, 419	
Rats, Inbred Strains.....	321, 344
Muscle Proteins.....	389
Mutation.....	3*, 20, 23*,
29*, 31, 34, 48, 78, 95, 113, 203*, 245, 250, 261, 277, 331, 333*,	
340, 341, 350*, 393, 398, 399, 405, 406, 408*, 409*, 411-413,	
418, 419, 421, 423	
Suppression, Genetic.....	3*, 113
Myeloblastosis Virus, Avian.....	53, 56, 118
Myelodysplastic Syndromes.....	116, 121, 126,
129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*,	
161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*,	
178, 182*, 183*, 186*, 242, 243, 245*, 246*, 251, 253, 298*,	
302*, 359, 386, 389, 407, 413, 416	

KEYWORDS

ABSTRACT NUMBERS

Leukemia, Myelocytic.....	10, 12, 104, 115, 116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174*, 175, 176*, 177*, 178, 182*, 183*, 186*, 193*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 298*, 302*, 307*, 308*, 310, 318, 336*, 359, 374*, 386, 389, 407, 413, 416
Leukemia, Myeloblastic.....	10, 12, 104, 115, 116, 121, 133, 134, 146*, 166*, 174*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 307*, 308*, 310, 318, 356*, 374*
Myeloproliferative Disorders.....	100, 134, 138*, 348*
Myristic Acids.....	173
Named Groups By Age.....	98, 118, 123, 125, 137, 140, 141, 147-149, 152, 153, 156, 157, 162, 164, 181, 184, 190, 202, 210, 218, 220-222, 225, 240, 248, 255, 269, 281, 283, 298, 315, 320, 326, 335, 336, 349, 415
Adolescence.....	98, 125, 137, 141, 164, 320, 326
Adult.....	118, 123, 125, 137, 140, 141, 147, 148, 149, 152, 156, 157, 162, 164, 181, 184, 190, 202, 210, 218, 220, 221, 222, 225, 240, 248, 255, 269, 281, 283, 298, 326, 335, 336, 349
Aged.....	125, 137, 140, 157, 181, 190, 218, 220, 221, 225, 248, 283, 326, 336, 349
Middle Age.....	125, 137, 140, 141, 148, 149, 152, 157, 162, 181, 190, 220-222, 248, 269, 281, 283, 326, 335, 349
Child.....	125, 137, 153, 156, 184, 269, 315, 320, 326, 415
Neoplasm Invasiveness.....	421
Neoplasm Metastasis.....	202, 260*, 272, 294, 326, 404
Neoplasm Proteins.....	11*, 82, 143, 145*, 165, 237*, 276, 300*, 323, 344*, 368
Myeloma Proteins.....	82
Neoplasm Staging.....	315, 320
Neoplasm Transplantation.....	279, 282, 299, 336, 350, 421
Neoplasms By Histologic Type.....	1*-9*, 10, 11*-29*, 30, 31*-36*, 37, 38*-50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*-95*, 96, 97*-99*, 102*, 103*, 104, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116*, 117, 118*-123*, 124, 125*-129*, 131*-134*, 136, 137*-143*, 145*-152*, 154*-162*, 164, 165*-178*, 180*-187*, 188, 190*, 195*, 196*, 197, 198*, 199*, 201, 202*-204*, 206*, 207, 208*, 211*, 213, 214*-226*, 228*-230*, 233*, 235*, 238*, 240*, 242*-246*, 247, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 262*, 263*, 264, 266*-263*, 269, 270*-278*, 280*-283*, 287*, 288*, 290*, 292*, 293*, 294, 296*-299*, 302*, 304*, 307*-313*, 315*, 317*-320*, 322*, 323, 324*-327*, 328, 329*-331*, 332, 334*-337*, 347*, 349*, 350, 355*, 356*, 357, 359*, 362, 363*, 364*, 367*-370*, 371-373, 374*, 379*, 380*, 382*, 385, 386, 389, 396, 398, 405, 407, 408, 413-416, 420, 421, 422*
Carcinoma.....	110, 180*, 190*, 264, 267*, 273*, 276*, 277*, 283*, 292*, 299*, 309*, 310, 330*, 331*, 332, 336*, 349*, 350, 355*, 359, 362, 363, 367*-369*, 371, 372, 396
Carcinoma, Mucinous.....	283*
Carcinoma, Oat Cell.....	110, 267*, 276*, 277*, 292*, 299*, 309*, 310, 330*, 332, 350, 355*, 396
Carcinoma, Squamous Cell.....	180, 273*, 332, 336*, 349*, 359, 362, 367*-369*, 371, 372
Carcinoma, Transitional Cell.....	190*
Leukemia.....	6*, 10, 12, 13*, 18*, 36*, 47*, 51, 88*, 91*, 94*, 95*, 97*, 98*, 99*, 104, 111, 115*, 116*, 121*, 123*, 125*, 126*, 128, 129, 133*, 134*, 136, 137*, 138*, 139*, 140*-143*, 145*, 146*, 147*-152*,

KEYWORDS

ABSTRACT NUMBERS

154*, 155*, 156*, 157*, 158*, 159*, 160*, 161*, 162*, 164, 165*-172*, 173*, 174*, 175*, 176*, 177*, 178*, 182*, 183*, 186*, 187*, 195*, 196*, 197, 198*, 206*, 207, 208*, 211*, 214, 218*, 218*, 219*, 20*, 221*, 222*, 223*-225*, 226*, 228*, 230*, 235*, 238*, 240*, 242*-244*, 245*, 246*, 247, 248, 251*, 253*, 256*, 257, 261, 262*, 263*, 264, 266*, 269, 270*, 271*, 274*, 275*, 280*, 281*, 288*, 296*, 297*, 298*, 302*, 307*, 308*, 310, 318, 319*, 359, 363, 374*, 385, 386, 389, 405, 407, 413, 414, 416, 422*	
Leukemia, Experimental.....	47*, 88*, 95*, 128, 136, 138*, 165*, 187*, 297*, 308, 405
Avian Leukosis.....	95*, 297*, 405
Leukemia, Hairy Cell.....	243
Leukemia, Lymphocytic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 111, 125*, 133, 134, 137*, 167*, 175, 178, 197, 198, 214, 218*, 219*, 221*, 222*, 225, 230*, 242, 251, 253, 296
Leukemia, Lymphoblastic.....	6*, 13*, 18*, 51, 91*, 94*, 97*, 98*, 125*, 133, 134, 137*, 167*, 178, 197, 198, 214, 230*, 242, 251, 253, 296
Leukemia, Monocytic.....	121, 134, 242, 251, 253
Leukemia, Myelocytic.....	10, 12, 104, 115, 116, 121, 126, 129, 133, 134, 139*-143*, 145*-152*, 154*, 155*, 157*-159*, 161*, 162*, 164, 166*, 168*-172*, 173, 174, 175, 176*, 177*, 178, 182*, 183*, 186*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 243, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 298*, 302*, 307*, 308*, 310, 318, 356*, 359, 374*, 386, 389, 407, 413, 416
Leukemia, Myeloblastic.....	10, 12, 134, 115, 116, 121, 133, 134, 146*, 166*, 174*, 195*, 196*, 198*, 226*, 228*, 235*, 238*, 240*, 242, 245*, 246*, 251, 253, 270*, 271*, 274*, 275*, 281*, 288*, 307*, 308*, 310, 318, 356*, 374*
Leukemia, Plasmacytic.....	248, 280*
Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33*, 34*, 35*, 36*, 37, 38*-48*, 49*, 50*, 51, 52*, 53*, 55*-59*, 60, 61*-63*, 64, 65*-67*, 68*, 69*-81*, 83*, 84*, 85*, 86, 87*, 89*, 90*, 92*, 93*, 96, 102*, 103*, 105, 106*-109*, 110, 111*, 112*, 113, 114, 115*, 116, 117, 118*, 119*, 120*-123*, 124, 125*, 126*, 127*-129*, 131*, 132*, 133*, 136, 175*, 199*, 201, 203*, 204*, 207, 208, 213, 214*, 215*, 216*, 217*, 218, 219*, 221*, 222*, 225*, 233*, 242*, 244*, 245*, 248*, 249, 251*, 253*, 255*, 256*, 257, 258*, 261, 263, 264, 266*, 296*, 297*, 374*, 396, 396, 405, 407, 408, 414, 416, 420, 422
Burkitt's Lymphoma.....	1*-9*, 10, 11*, 12*, 13, 14*-29*, 30, 31*, 32*, 33, 34*, 35*, 36, 37, 38*-50*, 51, 52*, 53*, 55*-57*, 60, 85*, 92, 105, 106*-109*, 110, 111*, 113, 114, 115*, 116, 117, 118*-120*, 121-124, 125*, 126, 129*, 131*, 132*, 133, 136, 175, 213, 225, 242, 249, 253, 258, 396, 407, 414, 416, 420
Hodgkin's Disease.....	253
Lymphoma, Giant Follicular.....	121, 215*, 217*
Lymphosarcoma.....	122, 203*, 204*, 374*
Plasmacytoma.....	20, 21*, 30, 31, 33, 37, 41*, 49, 51, 55*, 57, 58*, 59*, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*, 90*, 92, 110, 113, 117, 120, 122, 124, 127*-129*, 132*, 199*, 201, 204, 208, 218, 248*, 258, 396, 398
Multiple Myeloma.....	30, 57, 201, 248*
Melanoma.....	229*, 334*, 398
Neoplasms, Connective Tissue.....	184*, 185*, 287, 347*, 373, 416
Neoplasms, Embryonal and Mixed.....	202*, 318, 322*, 337*, 415
Neoplasms, Glandular Epithelial.....	93*, 272*, 282*,

KEYWORDS

ABSTRACT NUMBERS

283°, 290°, 294, 332, 335°, 357, 359°, 363°	
Adenocarcinoma.....	93°, 272°, 282°, 283°, 294, 332, 335°, 357, 359°, 363°
Carcinoma, Mucinous.....	283°
Hepatoma.....	290°
Neoplasms, Nervous Tissue.....	181°, 247, 249, 258, 261, 268°, 278°, 293°, 304°, 310°-313°, 315°, 317°-320°, 323, 324°-326°, 328, 329°, 333, 324°-327°, 328, 329°, 364°, 370°, 379°, 380°, 382°, 385, 386, 407, 415, 416
Glioma.....	268°, 310, 364°, 370°
Meningioma.....	181°
Neuroblastoma.....	247, 293°, 304°, 310°-313°, 315°, 317°-320°, 323, 324°-326°, 328, 329°, 379°, 382°, 385, 386, 415, 416
Neuroepithelioma.....	249, 258, 261, 278°, 326, 327°, 380°, 407, 415
Sarcoma.....	122, 184°, 185°, 188, 203°, 204°, 269, 287°, 347°, 373, 374°, 389, 398, 416, 421
Fibrosarcoma.....	347°, 373, 416
Lymphosarcoma.....	122, 203°, 204°, 374°
Sarcoma, Ewing's.....	184°, 185°
Sarcoma, Experimental.....	188, 287°, 389, 398, 421
Sarcoma, Osteogenic.....	287
Neoplasms By Site.....	9, 110, 124, 129, 180°, 181°, 190°, 194°, 202, 249, 259°, 260, 261, 267°, 272°, 273°, 276°-279°, 282°, 283°, 285°, 286°, 289, 290°-292°, 294°, 295°, 299°, 303°, 306°, 309°, 310, 326, 327°, 330°-332°, 335°, 336°, 338°-340°, 343°-346°, 349°-353°, 355°, 357°, 358°, 359, 361°, 362, 363°, 365°, 370°, 376°, 380°, 381°, 385, 386, 389, 396, 407, 415, 416
Breast Neoplasms.....	272°, 279°, 295°, 338°, 344°, 359, 361°, 365°, 381°, 416
Digestive System Neoplasms.....	180, 260, 282°, 283°, 285°, 286°, 289, 290°, 291°, 294°, 306°, 313, 331°, 339°, 343°, 353°, 357°, 358°, 359, 376°, 386, 389, 416
Gastrointestinal Neoplasms.....	180, 282°, 283°, 285°, 286°, 289, 294°, 306°, 310, 321°, 343°, 353°, 357°, 358°, 359, 376°, 386, 389, 416
Intestinal Neoplasms.....	285°, 286°, 289, 306°, 310, 353°, 357°, 358°, 359, 386, 389, 416
Colonic Neoplasms.....	285°, 286°, 289, 306°, 310, 353°, 357°, 358°, 359, 386, 389, 416
Stomach Neoplasms.....	180, 282°, 283°, 294°, 331°, 343°, 359, 376°
Liver Neoplasms.....	260, 290°, 291°
Pancreatic Neoplasms.....	339°
Endocrine Gland Neoplasms.....	335°, 345°, 346°, 352°
Eye Neoplasms.....	249, 261, 278°, 326, 327°, 380°, 407, 415
Mouth Neoplasms.....	180°, 363°
Nervous System Neoplasms.....	181°, 310, 370°
Skin Neoplasms.....	124, 202
Thoracic Neoplasms.....	110, 202, 267°, 273°, 276°, 277°, 292°, 299°, 303°, 309°, 310, 330°, 332°, 336°, 350°, 353°, 355°, 385, 396, 416
Respiratory Tract Neoplasms.....	110, 202, 267°, 273°, 276°, 277°, 292°, 299°, 303°, 309°, 310, 330°, 332°, 336°, 350°, 353°, 355°, 385, 396, 416
Lung Neoplasms.....	110, 202, 267°, 273°, 276°, 277°, 292°, 299°, 303°, 309°, 310, 330°, 332°, 336°, 350°, 353°, 355°, 385, 396, 416
Bronchial Neoplasms.....	273°
Urogenital Neoplasms.....	93°, 122, 190°, 194°, 259°, 335°, 340°, 349°, 351°, 362, 363, 416

KEYWORDS

ABSTRACT NUMBERS

Genital Neoplasms, Female.....	335°, 349°, 362, 363
Urologic Neoplasms.....	93°, 129, 190°, 194°, 259°, 340°, 351°, 416
Neoplasms, Connective Tissue.....	184°, 185°, 287, 347°, 373, 416
Neoplasms, Embryonal and Mixed.....	202°, 318, 322°, 337°, 415
Neoplasms, Experimental.....	39, 41, 47°, 55, 57, 84, 85, 87, 88°, 99, 90, 95°, 119°, 127°, 128, 130°, 132, 135, 136, 138°, 165°, 187°, 188, 201, 260, 287°, 291°, 297°, 304, 306, 308, 314, 344°, 349°, 352, 354°, 387, 389, 398, 401, 403, 405°, 408, 419°, 421, 423°
Leukemia, Experimental.....	47°, 88°, 95°, 128, 136, 138°, 165°, 187°, 297°, 308, 405
Avian Leukosis.....	95°, 297°, 405
Liver Neoplasms, Experimental.....	291°
Mammary Neoplasms, Experimental.....	344°
Sarcoma, Experimental.....	188, 287°, 389, 398, 421
Tumor Virus Infections.....	95°, 119°, 127°, 297°, 349°, 398, 405°, 408, 419°
Neoplasms, Glandular Epithelial.....	93°, 272°, 282°, 283°, 290°, 294, 332, 335°, 357, 359°, 363°
Adenocarcinoma.....	93°, 272°, 282°, 283°, 294, 332, 335°, 357, 359°, 363°
Carcinoma, Mucinous.....	283°
Hepatoma.....	290°
Neoplasms, Hormone-Dependent.....	344°
Neoplasms, Multiple Primary.....	380
Neoplasms, Nervous Tissue.....	181°, 247, 249, 258, 261, 268°, 278°, 293°, 304°, 310°-313°, 315°, 317°-320°, 323, 324°-327°, 328, 329°, 364°, 370°, 379°, 380°, 382°, 385, 386, 407, 415, 416
Glioma.....	268°, 310, 364°, 370°
Meningioma.....	181°
Neuroblastoma.....	247, 293°, 304°, 310°-313°, 315°, 317°-320°, 323, 324°-326°, 328, 329°, 379°, 382°, 385, 386, 415, 416
Neuroepithelioma.....	249, 258, 261, 278°, 326, 327°, 380°, 407, 415
Neoplasms, Radiation-Induced.....	393
Neoplastic Processes.....	6, 12°, 22, 31, 32, 33°, 51°, 75°, 80, 81, 92°, 95, 101°, 108, 116, 127°, 131, 132, 134, 135°, 137, 166, 168, 173, 179, 199°, 202, 204, 215, 221°, 233°, 239, 245°, 250, 260°, 263°, 265, 272, 294, 296°, 297, 299, 308°, 314°, 321°, 326, 331, 336, 339, 342°, 350°, 382°, 385, 393°, 398, 399, 401, 402°, 403-406, 408°, 410°, 411°, 412, 413, 414°, 416°, 419, 421, 423, 424°
Cell Transformation, Neoplastic.....	6, 12°, 22, 31, 32, 33°, 51°, 75°, 80, 81, 92°, 95, 101°, 108, 116, 131, 132, 134, 135°, 137, 166, 168, 173, 179, 199°, 204, 215, 221°, 233°, 239, 245°, 250, 263°, 265, 296°, 297, 299, 308°, 314°, 321°, 331, 336, 339, 342°, 350°, 382°, 385, 393°, 398, 399, 401, 402°, 403-406, 408°, 410°, 411°, 412, 413, 414°, 416°, 419, 421, 423, 424°
Cocarcinogenesis.....	127°, 393°
Neoplasm Invasiveness.....	421
Neoplasm Metastasis.....	202, 260°, 272, 294, 326, 404
Nephroblastoma.....	415
Nerve Growth Factors.....	191°
Nerve Tissue Proteins.....	191°
Nervous System Neoplasms.....	181°, 310, 370°
Neutrophils.....	174
Nitrosamines.....	180°
Nitroso Compounds.....	180°

KEYWORDS

ABSTRACT NUMBERS

Nucleic Acid Conformation.....	198*, 219, 367
Nucleic Acid Hybridization.....	2, 10-16, 20, 23, 27, 31, 34, 36, 37, 39-42, 51-57, 60, 61, 64, 68, 73, 76, 84-86, 89, 93, 98, 138, 140, 141, 149-150, 152, 156, 158, 159, 161, 163, 166-168, 170, 171, 176, 187-189, 191-195, 197, 201, 203, 207, 209, 211, 213, 225, 228, 230, 232, 233, 236-240, 270, 271, 278, 280, 288-290, 293-296, 304, 305, 308, 316, 318, 326, 327, 331, 334, 337, 346, 352-359, 364, 366, 370-372, 374, 395, 399
Nucleic Acid Renaturation.....	268, 316
Nucleic Acids.....	2*, 3, 5, 8, 11*, 12, 13, 17, 20, 22, 25, 26*, 29, 34, 37, 3*, 41*, 44, 48, 49, 52, 55, 56, 57*, 59*, 63, 64*, 69, 73*, 76, 77, 81*, 83-85, 86*, 89*, 90*, 95-97, 99, 104*, 113, 117, 123, 124, 136, 138-141, 146, 148, 149*, 150-153, 158*, 159, 161, 162, 165, 166, 170, 172, 173, 176, 181, 189, 194, 198*, 201, 204*, 207, 209, 215-217, 224, 225, 228, 233*, 234, 236, 237, 250, 252*, 257*, 267, 269, 271*, 272-275, 278*, 280-282, 285-287, 291, 292-294, 296, 298*, 303, 306*, 308*, 309-312, 313*, 314, 315, 317, 321, 322, 324-326, 329, 330*, 332, 333, 335, 336, 339, 341, 342, 343*, 345, 346*, 348, 351*, 352, 354*, 355, 356, 359, 360, 361*, 363, 365, 366*, 367*, 368, 370, 371, 372*, 374, 377, 378, 379*, 383-386, 388*, 389, 390, 398, 401, 403, 404, 410, 411, 413, 414, 416-418, 420, 422*
DNA.....	3, 5, 8, 13, 20, 26*, 29, 37, 39*, 41*, 44, 55, 56, 57*, 59*, 61, 69, 77, 81*, 83, 84, 85, 86*, 89*, 90*, 97, 99, 104*, 113, 117, 123, 124, 136, 138, 140, 141, 148, 150, 151, 152, 153, 159, 161, 165, 170, 176, 181, 189, 194, 198*, 201, 204*, 207, 209, 215, 217, 224, 225, 228, 233*, 236, 237, 250, 252*, 257*, 267, 269, 271*, 273, 274, 275, 278*, 281, 285-287, 290, 293, 294, 296, 298*, 303, 307*, 308*, 309-312, 313*, 315, 321, 326, 329, 330*, 332, 335, 336, 339, 341, 343*, 345, 346*, 351*, 354*, 356, 359, 360, 361*, 363-366, 367*, 370, 371, 372*, 374, 377, 378, 379*, 383, 384, 386, 388*, 389, 390, 398, 401, 403, 404, 410, 411, 413, 414, 416, 417, 420, 422*
DNA, Bacterial.....	404
DNA, Neoplasm.....	5, 8, 20, 26*, 39*, 41, 55, 56, 57*, 59*, 69, 81*, 84, 85, 89*, 90*, 97, 99, 124, 138, 141, 150, 153, 161, 165, 170, 194, 201, 204*, 215, 225, 233*, 257*, 267, 269, 271*, 273, 274, 281, 285-287, 294, 298*, 303, 307*, 308*, 309-312, 315, 321, 326, 329, 330*, 332, 335, 336, 343*, 345, 346*, 351*, 354*, 356, 361*, 363, 366, 367*, 370, 374, 372, 379*, 389, 398, 403, 410, 411, 413, 420, 422*
DNA, Recombinant.....	44, 56, 86*, 123, 138, 152, 176, 231, 217, 224, 225, 252*, 377, 384, 414, 417
DNA, Viral.....	99, 201, 296, 359, 404, 413, 416, 417
RNA.....	2*, 11*, 12, 17, 22, 25, 34, 41*, 48, 49, 52, 64*, 73*, 76, 90*, 95-97, 104, 113, 139, 141, 146, 148, 149*, 158*, 162, 166, 172, 173, 176, 201, 204, 216, 217, 234, 257, 272-274, 280, 282, 286, 287, 290, 292, 293, 296, 303, 306*, 309, 314, 317, 321, 322, 324, 325, 329, 330, 333, 336, 341, 342, 348, 352, 355, 363, 364, 366*, 367, 368, 371, 372, 385, 417, 418
RNA, Messenger.....	2*, 11*, 17, 22, 25, 34, 48, 49, 64*, 73*, 95, 96, 104, 113, 139, 149*, 166, 172, 173, 176, 201, 216, 217, 234, 267, 280, 286, 287, 292, 293, 309, 314, 317, 324, 325, 336, 341, 363, 364, 366*, 367, 368, 372, 385
Codon.....	48
RNA, Neoplasm.....	12, 41*, 52, 64*, 73*, 76, 90*, 97, 141, 146, 158*, 162, 201, 204, 216, 217, 272-274, 286, 287, 293, 303, 306*, 309, 317, 321, 322, 330, 348, 352, 368, 385
RNA, Ribosomal.....	418
RNA, Viral.....	296, 417
Nucleolus Organizer Region.....	138*
Nucleoproteins.....	8*-10*, 26*, 27*, 60*, 253, 267, 275*
Nucleosides.....	274

KEYWORDS

ABSTRACT NUMBERS

Nucleotides.....	46, 77, 217, 280, 286, 309, 329, 331, 332, 342, 355, 371, 400, 403
Deoxyribonucleotides.....	332
Polynucleotides.....	46, 77, 217, 280, 286, 309, 329, 331, 342, 355, 371
Oligonucleotides.....	77, 331
Polyribonucleotides.....	46, 217, 280, 286, 309, 329, 342, 355, 371
Purine Nucleotides.....	400, 403
Ribonucleotides.....	400, 403
Oils.....	275
Ointment Bases.....	127, 128
Oligodeoxyribonucleotides.....	77
Oligo peptide.....	144
Oncogene Proteins, Viral.....	105, 212*, 363*, 400*
Oncogenes.....	1, 2*-14*, 15, 17*-21*, 22, 23*-37*, 38, 39*-42*, 43, 44*, 46*, 48*-56*, 58*, 59*, 60*-68*, 70*-74*, 75, 76*-78*, 79, 80*-93*, 97*-99*, 100, 101*-105*, 106, 107, 108*, 109, 110*-115*, 116-118, 119*, 120, 122*, 123, 124*, 126, 127*, 128*, 130*-132*, 135*, 137, 138*, 139*, 140, 141*-144*, 145, 146*-151*, 152*, 153*, 154, 155, 156*, 157, 158*, 159*, 162*, 163*, 164, 165*-169*, 171*, 172, 173*-175*, 177, 178*, 179, 181*-183*, 186*, 187*, 189*, 191*, 192*, 194*, 195*, 196, 197*, 198, 199*-205*, 206, 208, 211*-214*, 216, 223, 226*-228*, 231*, 232*-234*, 239*, 240*, 242, 243*-245*, 246-248, 250, 251, 253, 255-257, 259, 260*, 261, 264, 265, 267*, 268*, 269*, 271*-275*, 277*, 279*-298*, 299, 300*-306*, 309*, 310*-312*, 313, 314*-329*, 330*, 331*-341*, 343*, 344, 345*, 346*, 348*-353*, 355*-358*, 359*, 360*-363*, 371, 373*-375*, 376*, 377*, 378*, 379, 380, 381*, 382, 383*, 385*, 386*, 387, 388, 396*, 398*, 399*, 400*-403*, 404, 405*, 406*, 408*, 409, 410*-413*, 415*-420*, 422, 423*
Proto-Oncogenes.....	59*, 137, 138*, 152*, 156*, 197*, 212*, 231*, 268*, 269*, 309*, 330*, 359*, 363*, 376*, 399*, 400*
Oncogenic Viruses.....	12, 32, 33, 43, 51, 53-56, 92*, 101, 105*, 110, 118, 119, 122, 123, 127*, 128, 132, 136*, 138, 143*, 144, 163*, 166, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 236, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 349, 351, 353*, 362*, 371, 373, 375*, 383*, 393, 396, 398, 400, 401, 403, 405, 408, 410, 412-414, 415, 416, 417, 418, 419*, 420*, 423
DNA Tumor Viruses.....	12, 32, 43, 51, 101, 110, 132, 136, 166, 236, 349, 396, 416
Epstein-Barr Virus.....	12, 32, 43, 51, 110, 132, 166, 396, 416
Papovaviridae.....	101, 236, 349
Retroviridae.....	33, 53-56, 95*, 105*, 118, 119, 122, 123, 127*, 128, 136, 138, 143*, 144, 163*, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 351, 353*, 362*, 371, 373, 375*, 383*, 398, 400, 403, 405, 408, 410, 412-414, 416, 419*, 420*, 423
Avian Leukosis-Sarcoma Viruses.....	53-56, 118, 127, 212*, 231*, 239, 296*, 297*, 305*, 307*, 362*, 371, 373, 403, 405, 416
Avian Leukosis Viruses.....	53, 54, 55, 56, 118, 122, 212*, 296*, 297*, 305*, 307*, 362*, 371, 405, 416
Erythroblastosis Virus, Avian.....	212*, 362*, 371
Myeloblastosis Virus, Avian.....	53, 56, 118
Avian Sarcoma Viruses.....	231*, 239, 373, 403
C-Type Viruses.....	119
Feline Fibrosarcoma Virus.....	241
Feline Leukemia Virus.....	99*
Human T-Cell Leukemia Virus.....	220, 243
Mouse Tumor Viruses.....	54, 122, 127,

KEYWORDS	ABSTRACT NUMBERS
128, 138, 143*, 144, 16*, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416	
Mammary Cancer Virus.....	416
Mouse Leukemia Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 203*, 204, 241, 284*, 348, 383
Abelson Leukemia Virus.....	122, 127, 128, 138, 143*, 144, 163, 168, 169*, 204, 241, 284*
Friend Virus.....	348
Moloney Leukemia Virus.....	54, 203*, 383
Mouse Sarcoma Viruses.....	197*, 351, 383*, 375, 398, 416
Simian Sarcoma Viruses.....	163, 187*, 188*
Oogenesis.....	384
Operon.....	23-25, 50, 65*, 70, 80, 82, 129, 292
Organophosphorus Compounds.....	144
Ovarian Diseases.....	335*
Ovarian Neoplasms.....	335*
Ovary.....	93, 196, 354, 377
Oxidoreductases.....	174, 377, 387, 389, 393, 394*
Pancreatic Diseases.....	339*
Pancreatic Neoplasms.....	339*
Papillomaviruses.....	349
Papovaviridae.....	101, 236, 349
Paraproteinemias.....	30, 57, 201, 248*
Paraproteins.....	82
Pathologic Processes.....	6, 12*, 22, 31, 32, 33*, 51*, 75*, 80, 81, 92*, 95, 101*, 108, 116, 127*, 131, 132, 134, 135*, 137, 166, 168, 173, 179, 199*, 204, 215, 221*, 233*, 239, 245*, 250, 263*, 265, 296*, 297, 299, 308*, 314*, 321*, 331, 336, 339, 342*, 350*, 382*, 385, 393*, 398, 399, 401, 402*, 403, 405, 406, 408*, 410*, 411*, 412, 413, 414*, 416*, 419, 421, 423, 424*
Cell Transformation, Neoplastic.....	6, 12*, 22, 31, 32, 33*, 51*, 75*, 80, 81, 92*, 95, 101*, 108, 116, 131, 132, 134, 135*, 137, 166, 168, 173, 179, 199*, 204, 215, 221*, 233*, 239, 245*, 250, 263*, 265, 296*, 297, 299, 308*, 314*, 321*, 331, 336, 339, 342*, 350*, 382*, 385, 393*, 398, 399, 401, 402*, 403, 405, 406, 408*, 410*, 411*, 412, 413, 414*, 416*, 419, 423, 424*
Cocarcinogenesis.....	127*, 393*
Neoplasm Invasiveness.....	421
Pedigree.....	181, 252
Peptides.....	15*, 139, 144, 165, 183*, 364, 365*, 368, 369*, 371, 372, 400, 402, 403, 412
Epidermal Growth Factor-Urogastrone.....	364, 365*, 368, 369*, 371, 372
Oligopeptides.....	144
Peptide Fragments.....	168, 372
Platelet-Derived Growth Factor.....	139, 183*, 400, 402, 403, 412
Petroleum.....	127, 128
Phagocytes.....	174, 234
Pharmaceutical Aids.....	127, 128, 344
Phenothiazines.....	248
Phenotype.....	6, 12, 137, 138, 226, 242, 247, 248, 251, 259, 269, 271, 306*, 314, 357, 390, 421, 422
Dosage Compensation (Genetics).....	422
Genetic Marker.....	137, 138, 226, 242, 247, 248, 251, 259, 306*, 357, 421
Phenylketonuria.....	252
Philadelphia Chromosome.....	137*, 139, 141*, 142, 148, 149*, 152*, 157*, 172*, 174*, 242, 246, 253

KEYWORDS	ABSTRACT NUMBERS
Phorbol Esters.....	275
Phorbols.....	275
Phosphatases.....	8-10, 13, 18, 23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383
Phosphodiesterases.....	8-10, 13, 18, 23, 25-27, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 75, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 267, 278, 280, 284, 290, 323, 333, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383
DNA Restriction Enzymes.....	8, 10, 13, 25, 26, 36, 44, 49, 51, 55, 60, 62, 65, 68, 70-73, 76, 84, 86, 97-99, 102-104, 140, 141, 150, 151, 154, 158, 161, 169, 172, 188, 194, 196, 198, 203, 224, 233, 237, 278, 280, 284, 290, 323, 337, 340, 342, 350, 352, 365, 366, 371, 377, 378, 383
Deoxyribonuclease I.....	8, 10, 27, 60, 267, 284
Deoxyribonucleases.....	9
Endodeoxyribonucleases.....	26
Endonucleases.....	18, 23, 65, 70, 72, 76, 284
Ribonuclease, Pancreatic.....	333
Phosphoproteins.....	144*, 165, 237*, 287*, 301*, 368
Phosphorus.....	301
Phosphorus Isotopes.....	301
Phosphorus Radioisotopes.....	301
Phosphorylation.....	143, 144, 173
Phosphoserine.....	144
Phosphotransferases.....	137*, 143*, 144*, 145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411
Phosphotransferases, ATP.....	137*, 143*, 144*, 145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411
Protein Kinases.....	137*, 143*, 144*, 145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411
Protein-Tyrosine Kinase.....	156, 363, 400
Phylogeny.....	401
Physics.....	2, 11, 299, 342
Phytohemagglutinins.....	307
Pigments.....	317*, 318*
Placenta.....	198, 383
Plant Proteins.....	307
Plants, Edible.....	404
Plasmacytoma.....	20, 21*, 30, 31, 33, 37, 41*, 49, 51, 55*, 57, 58*, 59*, 61*-63*, 64, 65*-81*, 83*-85*, 86, 87*, 89*, 90*, 92, 110, 113, 117, 120, 122, 124, 127*-129*, 132*, 199*, 201, 204, 208, 218, 248*, 258, 396, 398
Multiple Myeloma.....	30, 57, 201, 248*
Plasmids.....	101, 163, 188, 197, 205, 346, 352, 377
Plastics.....	128
Platelet-Derived Growth Factor.....	139, 183*, 400, 402, 403, 412
Pleural Diseases.....	299
Pleural Effusion.....	299
Ploidies.....	242, 260, 422
Poly A.....	46, 217, 280, 286, 309, 329, 342, 355, 371
Polycythemia Vera.....	134
Polymers.....	128, 344

KEYWORDS	ABSTRACT NUMBERS
Polymorphism (Genetics).....	181, 253, 269, 340
Polynucleotides.....	46, 77, 217, 280, 286, 309, 329, 331, 342, 355, 371
Clinonucleotides.....	77, 331
Polyrhonucleotides.....	46, 217, 280, 286, 309, 329, 342, 355, 371
Polyomaviruses.....	101, 236
Postoperative Complications.....	243
Poultry.....	122, 212, 296, 297, 301, 358, 363, 392, 398, 413, 419
Chickens.....	122, 212, 296, 297, 301, 358, 363, 392, 398, 413, 419
Precancerous Conditions.....	100, 138*, 281, 348*, 422
Precipitin Tests.....	143
Pregnancy.....	198, 377
Pregnancy Proteins.....	270
Preleukemia.....	281, 422
Primates.....	415
Probability.....	121, 254
Prognosis.....	242, 253, 259, 272, 312, 320, 326
Promoter Regions (Genetics).....	64, 66, 76*
Protein Binding.....	26
Protein Kinases.....	137*, 143*, 144*, 145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411
Protein-Tyrosine Kinase.....	156, 363, 400
Proteins.....	4*, 7*-11*, 14*, 17*, 18, 19, 22, 24*, 25, 26*, 27*, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 60*-62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 119*, 120, 123, 127, 129, 130*, 131, 137, 139, 143, 144*, 145*, 165, 170*, 173, 183*, 191*, 207*, 212*, 215-217, 218*, 219, 222, 223, 230*, 237*, 238*, 240, 243, 253, 255*, 267, 270*, 275*, 276, 287*, 289*, 300*, 301*, 307, 309*, 323, 342, 344*, 359, 360*-372*, 373, 377*, 399, 390, 396, 400*, 401-403, 411-413
Blood Proteins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 139, 170*, 183*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 400, 402, 403, 412, 413
Immunoproteins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 151, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 253*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215

KEYWORDS	ABSTRACT NUMBERS
75, 86, 90	
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 253*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Platelet-Derived Growth Factor.....	139, 183*, 400, 402, 403, 412
Serum Globulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Beta Globulins.....	93
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 253*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215

102

KEYWORDS

ABSTRACT NUMBERS

Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Carrier Proteins.....	93, 400
Contractile Proteins.....	389
Cytoskeletal Proteins.....	389
Globulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 289*, 396, 413
Serum Globulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Beta Globulins.....	93
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 86, 215
Immunoglobulins, Fc.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112, 120, 170*
Paraproteins.....	82
Thyroglobulin.....	289*
Glycoproteins.....	289*

KEYWORDS

ABSTRACT NUMBERS

Interferons.....	243
Iodoproteins.....	289*
Membrane Proteins.....	93, 230*, 344, 359, 360*-362*, 363, 364*-372*, 400, 401, 411
Receptors, Endogenous Substances.....	93, 230*, 344, 359, 360*-362*, 363, 364*-372*, 400, 401, 411
Guanine Nucleotide Regulatory Protein.....	400
Receptors, Insulin.....	230*
Receptors, Steroid.....	344
Metalloproteins.....	93
Neoplasm Proteins.....	11*, 82, 143, 145*, 165, 237*, 276, 300*, 323, 344*, 368
Myeloma Proteins.....	82
Nerve Tissue Proteins.....	191*
Nucleoproteins.....	8*-10*, 26*, 27*, 60*, 253, 267, 275*
Phosphoproteins.....	144*, 165, 237*, 287*, 301*, 368
Plant Proteins.....	307
Pregnancy Proteins.....	270
Proto-Oncogene Proteins, Cellular.....	137, 212*, 270*, 309*, 359, 363*, 400*
Recombinant Proteins.....	243, 363
Transcription Factors.....	119*
Viral Proteins.....	105, 143, 173, 212*, 238*, 363*, 373, 377*, 400*
Proto-Oncogenes.....	59*, 137, 138*, 152*, 156*, 197*, 212*, 231*, 268*, 269*, 309*, 330*, 359*, 363*, 376*, 399*, 400*
Protozoa.....	384
Public Health.....	299
Publications.....	257
Purine Nucleosides.....	274
Purine Nucleotides.....	400, 403
RNA.....	2*, 11*, 12, 17, 22, 25, 34, 41*, 48, 49, 52, 64*, 73*, 76, 90*, 95-97, 104, 113, 139, 141, 146, 148, 149*, 158*, 162, 166, 172, 173, 176, 201, 204, 216, 217, 234, 267, 272-274, 280, 282, 286, 287, 290, 292, 293, 296, 303, 306*, 309, 314, 317, 321, 322, 324, 325, 329, 330, 333, 336, 341, 342, 348, 352, 355, 363, 364, 366*, 367, 368, 371, 372, 385, 417, 418
RNA, Messenger.....	2*, 11*, 17, 22, 25, 34, 48, 49, 64*, 73*, 95, 96, 104, 113, 139, 149*, 166, 172, 173, 176, 201, 216, 217, 234, 267, 280, 286, 287, 292, 293, 309, 314, 317, 324, 325, 336, 341, 363, 364, 366*, 367, 368, 372, 385
Codon.....	48
RNA, Neoplasm.....	12, 41*, 52, 64*, 73*, 76, 90*, 97, 141, 146, 158*, 162, 201, 204, 216, 217, 272-274, 286, 287, 293, 303, 306*, 309, 317, 321, 322, 330, 348, 352, 368, 385
RNA, Ribosomal.....	418
RNA, Viral.....	296, 417
RNA Processing, Post-Transcriptional.....	64*
RNA Virus Infections.....	95*, 220*, 243, 297*, 405, 412*
RNA Viruses.....	33, 53, 54*, 55, 56, 99*, 105*, 118, 119, 122, 123, 127*, 128, 136, 138, 143*, 144, 163*, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 351, 353*, 362*, 371, 373, 375*, 383*, 398, 400, 403, 405, 408, 410, 412-414, 416, 419*, 420*, 423
RNA Rodent Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416
Mouse Tumor Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416

KEYWORDS

ABSTRACT NUMBERS

Mammary Cancer Virus.....	416
Mouse Leukemia Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 203*, 204, 241, 284*, 348, 383
Abelson Leukemia Virus.....	122, 127, 128, 138, 143*, 144, 163, 168, 169*, 204, 241, 284*
Friend Virus.....	348
Moloney Leukemia Virus.....	54, 203*, 383
Mouse Sarcoma Viruses.....	197*, 351, 353*, 375, 398, 416
Retroviridae.....	33, 53-56, 99*, 105*, 118, 119, 122, 123, 127*, 128, 136, 138, 143*, 144, 163*, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 351, 353*, 362*, 371, 373, 375*, 383*, 398, 400, 403, 405, 408, 410, 412-414, 416, 419*, 420*, 423
Avian Leukosis-Sarcoma Viruses.....	53-56, 118, 122, 212*, 231*, 239, 296*, 297*, 305*, 307*, 362*, 371, 373, 403, 405, 416
Avian Leukosis Viruses.....	53, 54, 55, 56, 118, 122, 212*, 296*, 297*, 305*, 307*, 362*, 371, 405, 416
Erythroblastosis Virus, Avian.....	212*, 362*, 371
Myeloblastosis Virus, Avian.....	53, 56, 118
Avian Sarcoma Viruses.....	231*, 239, 273, 403
C-Type Viruses.....	119
Feline Fibrosarcoma Virus.....	241
Feline Leukemia Virus.....	99*
Human T-Cell Leukemia Virus.....	220, 243
Mouse Tumor Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416
Mammary Cancer Virus.....	416
Mouse Leukemia Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 203*, 204, 241, 284*, 348, 383
Abelson Leukemia Virus.....	122, 127, 128, 138, 143*, 144, 163, 168, 169*, 204, 241, 284*
Friend Virus.....	348
Moloney Leukemia Virus.....	54, 203*, 383
Mouse Sarcoma Viruses.....	197*, 351, 353*, 375, 398, 416
Simian Sarcoma Viruses.....	163, 187*, 188*
RNA, Messenger.....	2*, 11*, 17, 22, 25, 34, 48, 49, 64*, 73*, 95, 96, 104, 113, 139, 149*, 166, 172, 173, 176, 201, 216, 217, 234, 267, 280, 286, 287, 292, 293, 309, 314, 317, 324, 325, 336, 341, 363, 364, 366*, 367, 368, 372, 385
Codon.....	48
RNA, Neoplasm.....	12, 41*, 52, 64*, 73*, 76, 90*, 97, 141, 146, 158*, 162, 201, 204, 216, 217, 272-274, 286, 287, 293, 303, 306*, 309, 317, 321, 322, 330, 348, 352, 368, 385
RNA, Ribosomal.....	418
RNA, Viral.....	296, 417
Rabbits.....	179
Radiation.....	299, 342
Radiation Dosage.....	299
Radiation Injuries.....	393
Radiation, Ionizing.....	342
Radioisotopes.....	193, 239, 301
Radiologic Health.....	299
Radiometry.....	299
Rats.....	32, 88, 101, 130, 138, 179, 291, 314, 321, 344, 354, 363, 389, 392, 398, 410, 413, 417, 419
Rats, Inbred Strains.....	321, 344

KEYWORDS

ABSTRACT NUMBERS

Rats, Inbred F344.....	321
Receptors, Antigen.....	206*-210*, 255*
Receptors, Antigen, T-Cell.....	206*-210*, 255*
Receptors, Endogenous Substances.....	93, 230*, 344, 359, 360*-362*, 363, 364*-372*, 400, 401, 411
Guanine Nucleotide Regulatory Protein.....	400
Receptors, Insulin.....	230*
Receptors, Steroid.....	344
Receptors, Estrogen.....	344
Receptors, Immunologic.....	206*-210*, 255*
Receptors, Progesterone.....	344
Recombinant Proteins.....	243, 363
Recombination, Genetic.....	7*, 24, 34, 62, 70, 90*, 91*, 100, 102, 148, 176, 193, 203, 216, 219, 233*, 250*, 258, 268, 277, 321, 357*, 375, 386, 388, 393*, 402, 404, 408, 413
Crossing Over (Genetics).....	102, 357*, 388, 393*
DNA Insertion Elements.....	62, 193, 203, 250, 258, 408
Genetic Vectors.....	321, 404
Reference Values.....	36
Repetitive Sequences, Nucleic Acid.....	71, 200, 316, 353, 383, 401
Reproduction.....	198, 322, 377, 384
Research.....	404, 418
Research Design.....	418
Respiratory Tract Neoplasms.....	110, 202, 267*, 273*, 276*, 277*, 292*, 299*, 303*, 309*, 310, 330*, 332*, 336*, 350*, 353*, 355*, 385, 396, 416
Lung Neoplasms.....	110, 202, 267*, 273*, 276*, 277*, 292*, 299*, 303*, 309*, 310, 330*, 332*, 336*, 350*, 353*, 355*, 385, 396, 416
Bronchial Neoplasms.....	273*
Reticuloendothelial System.....	234
Retinoblastoma.....	249, 258, 261, 278*, 326, 327*, 380*, 407, 415
Retinoids.....	317*, 318*
Retrospective Studies.....	125
Retroviridae.....	33, 53-56, 99*, 105*, 118, 119, 122, 123, 127*, 128, 136, 138, 143*, 144, 163*, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 351, 353*, 362*, 371, 373, 375*, 383*, 398, 400, 403, 405, 408, 410, 412-414, 416, 419*, 420*, 423
Avian Leukosis-Sarcoma Viruses.....	53-56, 118, 122, 212*, 231*, 239, 296*, 297*, 305*, 307*, 362*, 371, 373, 403, 405, 416
Avian Leukosis Viruses.....	53, 54, 55, 56, 118, 122, 212*, 296*, 297*, 305*, 307*, 362*, 371, 405, 416
Erythroblastosis Virus, Avian.....	212*, 362*, 371
Myeloblastosis Virus, Avian.....	53, 56, 118
Avian Sarcoma Viruses.....	231*, 239, 373, 403
C-Type Viruses.....	119
Feline Fibrosarcoma Virus.....	241
Feline Leukemia Virus.....	99*
Human T-Cell Leukemia Virus.....	220, 243
Mouse Tumor Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416
Mammary Cancer Virus.....	416
Mouse Leukemia Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 203*, 204, 241, 284*, 348, 385

KEYWORDS

ABSTRACT NUMBERS

Abelson Leukemia Virus.....	122, 127, 128, 138, 143*, 144, 163, 168, 169*, 204, 241, 284*
Friend Virus.....	348
Moloney Leukemia Virus.....	54, 203*, 383
Mouse Sarcoma Viruses.....	197*, 351, 353*, 375, 398, 416
Simian Sarcoma Viruses.....	163, 187*, 188*
Retroviridae Proteins.....	212*
Retrovirus Infections.....	95*, 220*, 243, 297*, 405, 412*
Ribonuclease, Pancreatic.....	333
Ribonucleosides.....	274
Ribonucleotides.....	400, 403
Risk.....	121, 254
Rodentia.....	3, 17, 20, 21, 30-32, 37, 38, 41, 46, 49, 51, 53, 55-90, 92, 93, 100, 101, 113, 117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136-138, 142, 143, 159, 163, 170, 173, 177, 179, 180, 186-188, 192, 196, 197, 199, 201, 203, 204, 207-211, 218, 224, 225, 228, 230, 231, 233, 234, 236, 241, 245, 258, 279, 282, 284, 286, 287, 289, 291, 294, 296, 299, 300, 311, 314, 321, 322, 331, 336, 337, 344-346, 348, 350, 352, 354, 363, 366, 373, 377, 387, 389, 392, 394, 398, 410, 413, 417, 419
Cricetidae.....	38, 56, 67, 93, 159, 170, 180, 186, 192, 196, 211, 224, 230, 231, 234, 241, 354, 377, 389, 392, 394
Hamsters.....	38, 56, 67, 93, 159, 170, 180, 186, 192, 196, 211, 224, 230, 231, 234, 241, 354, 377, 389, 392, 394
Cricetulus.....	56, 93, 159, 170, 186, 192, 196, 211, 224, 230, 231, 354, 377, 392, 394
Mesocricetus.....	180
Muridae.....	3, 17, 20, 21, 30-32, 37, 38, 41, 46, 49, 51, 53, 55-90, 92, 100, 101, 113, 117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136-138, 142, 143, 159, 163, 173, 177, 179, 186-188, 192, 197, 199, 201, 203, 204, 207-210, 218, 224, 225, 228, 231, 233, 236, 241, 245, 258, 279, 282, 284, 286, 287, 289, 291, 294, 296, 299, 300, 311, 314, 321, 322, 331, 336, 337, 344-346, 348, 350, 352, 354, 363, 366, 373, 377, 387, 389, 392, 394, 398, 410, 413, 417, 419
Mice.....	3, 17, 20, 21, 30, 31, 37, 38, 41, 46, 49, 51, 53, 55-87, 89, 90, 92, 100, 113, 117, 118, 120, 122, 124, 127, 128*, 129, 130, 132, 136, 137, 142, 143, 159, 163, 173, 177, 179, 186-188, 192, 197, 199, 201, 203, 204, 207-210, 218, 224, 225, 228, 231, 233, 236, 241, 245, 258, 279, 282, 284, 286, 287, 289, 294, 296, 299, 300, 311, 314, 322, 331, 336, 337, 345, 346, 348, 350, 352, 354, 363, 366, 373, 377, 387, 392, 394, 398, 410, 413, 417, 419
Mice, Inbred Strains.....	41, 61, 68, 69, 71, 73, 77, 79, 81, 83, 127, 201, 203, 204, 284, 286, 296, 348, 350, 354
Mice, Inbred AKR.....	61, 68, 79
Mice, Inbred BALB C.....	41, 69, 71, 73, 77, 79, 81, 83, 127, 201, 203, 204, 284, 286, 296
Mice, Mutant Strains.....	279, 282, 299, 311, 314, 336, 350
Rats.....	32, 88, 101, 130, 138, 179, 291, 314, 321, 344, 354, 363, 389, 392, 398, 410, 413, 417, 419
Rats, Inbred Strains.....	321, 344
Rubidium.....	319
SV40 Virus.....	236
Salivary Gland Diseases.....	363*
Salivary Gland Neoplasms.....	363*
Sarcoma.....	122, 184*, 185*, 188, 203*, 204*, 269, 287*, 347*, 373, 374*, 389, 398, 416, 421
Fibrosarcoma.....	347*, 373, 416
Lymphosarcoma.....	122, 203*, 204*,

KEYWORDS

ABSTRACT NUMBERS

374*	
Sarcoma, Ewing's.....	184*, 185*
Sarcoma, Experimental.....	188, 287*, 389, 398, 421
Sarcoma, Osteogenic.....	287
Sarcoma, Yoshida.....	421
Science.....	30, 85, 113, 131, 135, 172*, 177, 245, 252, 383, 384, 393*, 404, 409*, 413, 418
Methods.....	252
Models, Theoretical.....	30, 85, 113, 131, 135, 172*, 177, 245, 383, 384, 393*, 409*, 413
Models, Biological.....	30, 85, 113, 131, 172*, 177, 245, 383, 384, 393*, 409*, 413
Models, Genetic.....	30, 85, 113, 172*, 177, 245, 383, 384, 393*, 409*, 413
Research.....	404, 418
Sea Urchins.....	249
Sequence Homology, Nucleic Acid.....	212, 309, 330, 363
Serine.....	144
Serodiagnosis.....	143
Serum Globulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*-87*, 89, 90*, 92, 93, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
Beta Globulins.....	93
Immunoglobulins.....	4*, 7*, 9, 14*, 17*, 18, 19, 22, 24*, 25, 27, 30, 33, 34, 35*, 37*, 38*, 40*, 42, 43*, 44*, 45*, 46*, 47*, 48, 50, 55*, 57*, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 77, 82*, 83*, 85*, 86*, 87*, 89, 90*, 92, 96*, 98*, 100*, 102, 105, 106*, 107*, 110, 111*, 112, 118, 120, 123, 127, 129, 130*, 131, 170*, 207*, 215-217, 218*, 219, 222, 223, 255*, 396, 413
IgA.....	89
IgM.....	34
Immunoglobulin Fragments.....	4*, 7*, 14*, 17*, 24*, 25, 27, 30, 35*, 37*, 38*, 40*, 42, 43*-47*, 48, 50, 55*, 57, 61*, 62*, 63, 66*, 67, 68*, 69, 70*, 71*, 74*, 75, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 112, 120, 123, 170*, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulin Constant Region.....	4*, 25, 45*, 75, 86, 90
Immunoglobulin Variable Region.....	48, 85, 215
Immunoglobulins, Fab.....	48, 86, 215
Immunoglobulins, Fc.....	4*, 25, 45*, 75, 86, 90
Immunoglobulins, Heavy Chain.....	4, 7*, 17*, 27, 30, 38*, 40*, 44*-47*, 48, 50, 55*, 57, 62*, 63, 67, 68*, 70*, 71*, 82*, 83*, 86, 87*, 89, 90, 92, 96*, 98*, 100*, 102, 111*, 120, 123, 207*, 215-217, 218*, 219, 222, 255*
Immunoglobulins, Alpha Chain.....	82*, 98*, 100*, 207*
Immunoglobulins, Gamma Chain.....	44*, 57, 63, 87*
Immunoglobulins, Mu Chain.....	7*, 17*, 40*, 45*, 57, 102
Immunoglobulins, J Chain.....	215
Immunoglobulins, Light Chain.....	14*, 24*, 25, 35*, 37*, 42, 43*, 61*, 66*, 69, 74*, 75, 111*, 112, 120, 170*
Immunoglobulins, Kappa Chain.....	14*, 25, 35*, 37*, 43*, 61*, 66*, 69, 74*, 75, 120
Immunoglobulins, Lambda Chain.....	24*, 42, 112,

KEYWORDS

ABSTRACT NUMBERS

120, 170*	
Paraproteins.....	82
Sex Behavior.....	43
Sex Chromosomes.....	249, 254, 306
Sex Factors.....	125
Simian Sarcoma Viruses.....	163, 187*, 188*
Sister Chromatid Exchange.....	357*, 388, 393*
Skin.....	301
Skin Neoplasms.....	124, 202
Slow-Reacting Substances.....	144
Sodium.....	319
Species Specificity.....	49, 79, 81, 84, 85, 346
Spermatocytes.....	227
Spermatozoa.....	227
Spleen.....	78
Splenectomy.....	243
Stains and Staining.....	1, 14, 16, 22, 35, 42, 61, 79*, 93, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 202, 208, 224, 226, 228, 229, 248*, 253, 254, 256, 259, 261, 262, 264, 285, 288, 302, 306, 313, 319, 357, 358, 374, 386, 421, 422
Chromosome Banding.....	1, 14, 16, 22, 35, 42, 61, 79*, 93, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 202, 208, 224, 226, 228, 229, 248*, 253, 254, 256, 259, 261, 262, 264, 285, 288, 302, 306, 313, 319, 357, 358, 374, 386, 421, 422
Statistics.....	121, 254
Stem Cells.....	17, 23, 101, 142, 174, 183, 188, 201, 226, 236, 245*, 270*, 284, 299, 322, 327, 341*, 342, 347, 373
Fibroblasts.....	17, 23, 76, 101, 142, 188, 192, 201, 226, 236, 284, 327, 341*, 342, 347, 373
L Cells.....	76, 192
Hematopoietic Stem Cells.....	183, 245*, 270*
Tumor Stem Cells.....	174, 299, 322
Stomach.....	376
Stomach Diseases.....	180, 282*, 283*, 294*, 331*, 343*, 359, 376*
Stomach Neoplasms.....	180, 281*, 283*, 294*, 331*, 343*, 359, 376*
Substrate Specificity.....	144
Sulfites.....	399
Sulfur.....	399
Sulfurous Acids.....	399
Suppression, Genetic.....	3*, 113
Syndrome.....	234
T Lymphocytes.....	33*, 79, 92*, 94, 125, 174, 206-208, 215, 221*, 222, 233, 253, 416
Technology, Medical.....	1, 14, 16, 22, 35, 42, 54, 61, 79*, 93, 101, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 201, 202, 208, 221, 224, 226, 228, 229, 248*, 253, 254, 256, 259-262, 264, 276, 285, 288, 299*, 302, 306, 313, 319, 347, 357, 358, 374, 386, 421, 422
Cytological Technics.....	1, 14, 16, 22, 35, 42, 54, 61, 79*, 93, 101, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 201, 202, 208, 221, 224, 226, 228, 229, 248*, 253, 254, 256, 259-262, 264, 276, 285, 288, 299*, 302, 306, 313, 319, 347, 357, 358, 374, 386, 421, 422
Autoradiography.....	54, 193, 201
Cell Fusion.....	101, 260, 347
Chromosome Banding.....	1, 14, 16, 22, 35, 42, 61, 79*, 93, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 202, 208, 224, 226, 228, 229, 248*, 253, 254, 256, 259, 261, 262, 264, 285, 288, 302, 306, 313, 319, 357, 358, 374, 386, 421, 422

KEYWORDS

ABSTRACT NUMBERS

Colony-Forming Units Assay.....	276, 299*
Histochemistry.....	221
Histological Technics.....	54, 193, 201, 221
Stains and Staining.....	1, 14, 16, 22, 35, 42, 61, 79*, 93, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 202, 208, 224, 226, 228, 229, 248*, 253, 254, 256, 259, 261, 262, 264, 285, 288, 302, 306, 313, 319, 357, 358, 374, 386, 421, 422
Chromosome Banding.....	1, 14, 16, 22, 35, 42, 61, 79*, 93, 116, 134, 157, 159, 164, 166, 167, 172, 176, 184, 185, 192, 193, 196, 197, 202, 208, 224, 226, 228, 229, 248*, 253, 254, 256, 259, 261, 262, 264, 285, 288, 302, 306, 313, 319, 357, 358, 374, 386, 421, 422
Technology, Pharmaceutical.....	2
Telangiectasis.....	179, 209, 210, 255*
Teratoma.....	202*, 318, 322*, 337*
Terpenes.....	127, 128, 275, 284, 317*, 318*
Testis.....	54, 322
Tetradecanoylphorbol Acetate.....	275
Tetrahydrofolate Dehydrogenase.....	377, 387, 389, 393
Tetrahymena.....	384
Thoracic Neoplasms.....	110, 202, 267*, 273*, 276*, 277*, 292*, 299*, 303*, 309*, 310, 330*, 332*, 336*, 350*, 353*, 355*, 385, 396, 416
Respiratory Tract Neoplasms.....	110, 202, 267*, 273*, 276*, 277*, 292*, 299*, 303*, 309*, 310, 330*, 332*, 336*, 350*, 353*, 355*, 385, 396, 416
Lung Neoplasms.....	110, 202, 267*, 273*, 276*, 277*, 292*, 299*, 303*, 309*, 310, 330*, 332*, 336*, 350*, 353*, 355*, 385, 396, 416
Bronchial Neoplasms.....	273*
Thyroglobulin.....	289*
Time.....	64, 301, 318
Time Factors.....	318
Trace Elements.....	319
Transcription Factors.....	113*
Transcription, Genetic.....	3, 5-7, 10*, 12, 17, 18*, 20, 21, 27, 29, 37*, 39*, 41*, 42*, 44, 45*, 46, 49*, 50, 60*, 63*, 64*, 73*, 76*, 81, 82, 84*, 85, 89, 95, 96*, 103-105, 108, 113, 123, 130, 139, 142, 146*, 150*, 158*, 162*, 166, 176, 177, 199, 201, 212, 216, 217, 233, 234, 243, 269, 271, 275*, 279, 290, 290, 292*, 295, 296, 333*, 337, 345, 348, 352, 355*, 403, 406, 408, 411
RNA Processing, Post-Transcriptional.....	64*
Transferases.....	137*, 143*, 144*, 145, 156, 165*, 173, 180*, 238*, 241, 361*, 363, 373, 389, 400, 401, 403, 411
Acyltransferases.....	180*
Aspartate Carbamoyltransferase.....	389
Phosphotransferases.....	137*, 143*, 144*, 145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411
Phosphotransferases, ATP.....	137*, 143*, 144*, 145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411
Protein Kinases.....	137*, 143*, 144*, 145, 156, 165*, 173, 238*, 241, 361*, 363, 373, 400, 401, 403, 411
Protein-Tyrosine Kinase.....	156, 363, 400
Transferrin.....	93
Transformation, Genetic.....	58, 95, 99*,

KEYWORDS

ABSTRACT NUMBERS

105, 108, 110, 114, 124, 132, 144, 165*, 173, 177, 179, 201, 233, 236, 284, 296*, 297, 300, 305*, 314, 321, 331, 340, 373*, 377, 388, 396, 398, 401, 406, 410, 411, 413, 416, 417, 419, 423	
Cell Transformation, Viral.....	95, 108, 110, 114, 132, 165*, 179, 236, 284, 296*, 297, 305*, 373*, 396, 401, 406, 413, 416, 419, 423
Transduction, Genetic.....	99*, 105, 144, 173, 398, 413
Transfection.....	58, 105, 124, 201, 233, 296, 300, 314, 321, 331, 340, 373, 377, 388, 410, 411, 416, 417
Translation, Genetic.....	103*, 104, 197, 272, 300, 305, 345, 403
Translocation (Genetics).....	1*, 2, 3, 4*-6*, 7, 8, 9*, 13*-20*, 22*, 23, 24, 25*, 26, 27*, 28, 29*-31*, 32, 33, 34*, 35*, 37*-39*, 40, 41, 42*, 44*, 45, 46*, 47*, 48, 49*, 50, 51*, 52*, 53, 54*-57*, 58, 59, 60*-63*, 64, 65*-69*, 70, 71*-79*, 80-82, 83*-85*, 87*-89*, 91, 92, 93*, 94-97, 98*, 102*, 103*, 106, 107*, 108-110, 111*-113*, 114-116, 117*-120*, 122, 123*, 124, 125, 126*, 127*, 128, 129*, 131*-133*, 134, 135*, 136, 137*, 138*, 139, 140, 141*, 142*, 144, 145, 147*, 148, 149*, 151*-153*, 154-156, 157*-162*, 164*, 168-170, 171*, 172*, 173, 174*, 175-177, 181*, 182, 183*-186*, 188, 192, 195*, 196*, 197, 202, 206*, 207, 208, 211*, 214*-219*, 221-223, 224*, 225*, 226-228, 229*, 230, 235, 238*, 239, 240*, 242, 243, 244*, 245, 246*, 247, 249, 251-253, 255*, 256, 258*, 261, 263-266, 288, 292*, 306*, 328, 366*, 367, 368*, 371, 374, 380, 385, 386, 396-402, 405-407, 409-413, 415-417, 419-422, 424*
Philadelphia Chromosome.....	137*, 139, 141*, 142, 148, 149*, 152*, 157*, 172*, 174*, 242, 246, 253
Transplantation.....	279, 350
Transplantation Immunology.....	307
Transplantation, Heterologous.....	279, 350
Tretinoin.....	317*, 318*
Trisomy.....	37, 129, 136, 258*, 281, 421
Tritium.....	193, 239
Tumor Stem Cell Assay.....	276, 299*
Tumor Stem Cells.....	174, 299, 322
Tumor Virus Infections.....	95*, 119*, 127*, 297*, 349*, 398, 405*, 408, 419*
Turkey.....	419
Tyrosine.....	165, 368
Urinary Tract.....	59, 81, 322
Urogenital Neoplasms.....	93*, 129, 190*, 194*, 259*, 335*, 340*, 349*, 351*, 362, 363, 416
Genital Neoplasms, Female.....	335*, 349*, 362, 363
Urologic Neoplasms.....	93*, 129, 190*, 194*, 259*, 340*, 351*, 416
Urologic Diseases.....	93*, 129, 190*, 194*, 259*, 340, 351*, 416
Uterine Diseases.....	349*
Uterine Neoplasms.....	349*
Variation (Genetics).....	25*, 31, 61*, 92, 181*, 260*, 292
Vascular Diseases.....	179, 209, 210, 255*
Vertebrate Viruses.....	12, 32, 33, 43, 51, 53, 54*, 55, 56, 99*, 101, 105*, 110, 118, 119, 122, 123, 127*, 128, 132, 136*, 138, 143*, 144, 163*, 166, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 236, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 349, 351, 353*, 362*, 371, 373, 375*, 383*, 393, 396, 398, 400, 401, 403, 405, 408, 410, 412-418, 419*, 420*, 423
DNA Viruses.....	12, 32, 43, 51, 101, 110, 132, 136, 166, 236, 349, 396, 416
DNA Tumor Viruses.....	12, 32, 43, 51, 101, 110, 132, 136, 166, 236, 349, 396, 416

KEYWORDS

ABSTRACT NUMBERS

Epstein-Barr Virus.....	12, 32, 43, 51, 110, 132, 166, 396, 416
Papovaviridae.....	101, 236, 349
Herpesviridae.....	12, 32, 43, 51, 110, 132, 166, 396, 416
Oncogenic Viruses.....	12, 32, 33, 43, 51, 53-56, 99*, 101, 105*, 110, 118, 119, 122, 123, 127*, 128, 132, 136*, 138, 143*, 144, 163*, 166, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 236, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 349, 351, 353*, 362*, 371, 373, 375*, 383*, 393, 396, 398, 400, 401, 403, 405, 408, 410, 412-414, 415, 416, 417, 418, 419*, 420*, 423
DNA Tumor Viruses.....	12, 32, 43, 51, 101, 110, 132, 136, 166, 236, 349, 396, 416
Epstein-Barr Virus.....	12, 32, 43, 51, 110, 132, 166, 396, 416
Papovaviridae.....	101, 236, 349
Retroviridae.....	33, 53-56, 99*, 105*, 118, 119, 122, 123, 127*, 128, 136, 138, 143*, 144, 163*, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 351, 353*, 362*, 371, 373, 375*, 383*, 398, 400, 403, 405, 408, 410, 412-414, 416, 419*, 420*, 423
Avian Leukosis-Sarcoma Viruses.....	53-56, 118, 122, 212*, 231*, 239, 296*, 297*, 305*, 307*, 362*, 371, 373, 403, 405, 416
Avian Leukosis Viruses.....	53, 54, 55, 56, 118, 122, 212*, 296*, 297*, 305*, 307*, 362*, 371, 405, 416
Erythroblastosis Virus, Avian.....	212*, 362*, 371
Myeloblastosis Virus, Avian.....	53, 56, 118
Avian Sarcoma Viruses.....	231*, 239, 373, 403
C-Type Viruses.....	119
Feline Fibrosarcoma Virus.....	241
Feline Leukemia Virus.....	99*
Human T-Cell Leukemia Virus.....	220, 243
Mouse Tumor Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416
Mammary Cancer Virus.....	416
Mouse Leukemia Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 203*, 204, 241, 284*, 348, 383
Abelson Leukemia Virus.....	122, 127, 128, 138, 143*, 144, 163, 168, 169*, 204, 241, 284*
Friend Virus.....	348
Moloney Leukemia Virus.....	54, 203*, 383
Mouse Sarcoma Viruses.....	197*, 351, 353*, 375, 398, 416
Simian Sarcoma Viruses.....	163, 187*, 188*
RNA Viruses.....	33, 53, 54*, 55, 56, 99*, 105*, 118, 119, 122, 123, 127*, 128, 136, 138, 143*, 144, 163*, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 351, 353*, 362*, 371, 373, 375*, 383*, 398, 400, 403, 405, 408, 410, 412-414, 416, 419*, 420*, 423
RNA Rodent Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416
Mouse Tumor Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416
Mammary Cancer Virus.....	416
Mouse Leukemia Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 203*, 204, 241, 284*, 348, 383
Abelson Leukemia Virus.....	122, 127, 128,

KEYWORDS

ABSTRACT NUMBERS

138, 143*, 144, 163, 168, 169*, 204, 241, 284*	
Friend Virus.....	348
Moloney Leukemia Virus.....	54, 203*, 383
Mouse Sarcoma Viruses.....	197*, 351, 353*, 375, 398, 416
Retroviridae.....	33, 53-56, 99*, 105*, 118, 119, 122, 123, 127*, 128, 136, 138, 143*, 144, 163*, 168, 169*, 173, 187*, 188*, 197*, 203*, 204, 212*, 220, 231*, 239, 241*, 243, 284*, 296*, 297*, 305*, 307*, 308, 348, 351, 353*, 362*, 371, 373, 378*, 383*, 398, 400, 403, 405, 408, 410, 412-414, 416, 419*, 420*, 423
Avian Leukosis-Sarcoma Viruses.....	53-56, 118, 122, 212*, 231*, 239, 296*, 297*, 305*, 307*, 362*, 371, 373, 403, 405, 416
Avian Leukosis Viruses.....	53, 54, 55, 56, 118, 122, 212*, 296*, 297*, 305*, 307*, 362*, 371, 405, 416
Erythroblastosis Virus, Avian.....	212*, 362*, 371
Myeloblastosis Virus, Avian.....	53, 56, 118
Avian Sarcoma Viruses.....	231*, 239, 373, 403
C-Type Viruses.....	119
Feline Fibrosarcoma Virus.....	241
Feline Leukemia Virus.....	99*

KEYWORDS

ABSTRACT NUMBERS

Human T-Cell Leukemia Virus.....	220, 243
Mouse Tumor Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 197*, 203*, 204, 241, 284*, 348, 351, 353*, 375, 383, 398, 416
Mammary Cancer Virus.....	416
Mouse Leukemia Viruses.....	54, 122, 127, 128, 138, 143*, 144, 163, 168, 169*, 173, 203*, 204, 241, 284*, 348, 383
Abelson Leukemia Virus.....	122, 127, 128, 138, 143*, 144, 163, 168, 169*, 204, 241, 284*
Friend Virus.....	348
Moloney Leukemia Virus.....	54, 203*, 383
Mouse Sarcoma Viruses.....	197*, 351, 353*, 375, 398, 416
Simian Sarcoma Viruses.....	163, 187*, 188*
Viral Proteins.....	105, 143, 173, 212*, 238*, 363*, 373, 377*, 400*
Virus Activation.....	127, 419
Virus Replication.....	127, 419
Vulvar Diseases.....	362, 363
Vulvar Neoplasms.....	362, 363
Weights and Measures.....	36
Wounds and Injuries.....	393

AUTHOR INDEX

AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS
Aaronson S.....	55	Bernheim A.....	13, 94, 197, 213	Chang EH.....	353, 354
Aaronson SA.....	189, 192, 340, 361, 400, 412	Berrebi A.....	162	Chattopadhyay SK.....	354
Abcarian FW.....	67	Bertness V.....	330	Chau E.....	278
Abou-Issa H.....	344	Bevan PC.....	248	Chen EY.....	305
Adams JM.....	33, 49, 62, 66, 71, 74, 83, 85, 92	Biedler JL.....	379, 391	Chen HL.....	138
Aden D.....	18, 20	Bilalstrom R.....	157	Chen KC.....	248
Adolph S.....	35	Birnie GD.....	271, 298	Cho-Chung YS.....	344
Aghai E.....	162	Birshtrian BK.....	72	Chorazy M.....	250
Aisenberg AC.....	120	Bishop JM.....	285, 287, 301, 304, 306, 314, 315, 322, 325, 326, 328, 352, 358	Chou CK.....	290
Akiyama T.....	360	Bjorkholm M.....	280	Chumakov IM.....	375, 383
Alabaster O.....	43	Blanchard JM.....	64	Clark AJ.....	367, 369, 371
Alitalo K.....	277, 281, 285, 287, 304, 306, 352, 357, 358, 386	Bleskau J.....	93	Clark WH Jr.....	229
Alitalo R.....	281	Blick M.....	91, 139	Clarkson B.....	3, 34
Almogueria C.....	333	Bodmer WF.....	241	Cleary ML.....	217
Alt FW.....	321, 324, 329	Bolger GB.....	181	Cline MJ.....	269, 359
Amagasaki T.....	220	Bockema D.....	160, 168, 171	Cohen BB.....	47
Arnautova TT.....	317	Bornkamm GW.....	35	Cohen MB.....	274
Amouroux J.....	273	Bos JL.....	351	Colby WW.....	305
Amesbaugh SC.....	189	Bottero L.....	97, 98	Cole MD.....	73, 77, 90
Anraku Y.....	339	Boyd JP.....	319	Coleman M.....	149
Aoyama N.....	138	Bradley C.....	93	Collard JG.....	202
Ar-Rushdi A.....	3, 5, 17, 18, 20, 37, 39, 50, 51, 137, 302	Bradley CM.....	196	Collins S.....	307
Arlinghaus R.....	143	Braithwaite AW.....	113	Collins SJ.....	145, 166
Armstrong G.....	43	Brathwaite MD.....	356	Cooper GM.....	233, 416
Astrin SM.....	36, 296, 297	Bregni M.....	56	Corcoran L.....	66
Atkin NB.....	190, 247	Bregula U.....	79	Corcoran LM.....	33, 62, 85
Augenlicht LH.....	286	Brisson O.....	279, 397	Cory S.....	33, 49, 62, 66, 71, 74, 83, 85, 92
Aurias A.....	185	Brianenden JE.....	15	Cosman J.....	214, 215, 219
Azizkhan JC.....	388	Brocas H.....	289	Cousseins L.....	372
Babonits M.....	61, 79	Brodeur G.....	304, 328	Cremer T.....	35
Baer R.....	29, 30, 31, 45, 48	Brodeur GM.....	310, 312, 313, 315, 320, 326	Crews S.....	89
Bagby GC Jr.....	270	Brooks BJ.....	330	Croce C.....	38
Baker MC.....	190	Brooks BJ Jr.....	309	Croce CM.....	3, 4, 5, 6, 16, 17, 18, 19, 20, 37, 39, 41, 42, 43, 50, 51, 56, 57, 58, 67, 102, 104, 111, 112, 114, 115, 117, 118, 119, 123, 137, 142, 167, 188, 206, 207, 210, 214, 215, 218, 219, 223, 224, 225, 227, 228, 235, 295, 302
Bakhsai A.....	216	Brown PC.....	394	Cunningham JM.....	32, 353
Balsan G.....	229, 319	Bruno M.....	97, 98	Curran T.....	377
Balsan-Malenbaum G.....	395	Bruns G.....	313, 329	Cuzin F.....	101
Ballantine M.....	4	Buffe D.....	185	Dalla Favera R.....	40, 188, 302, 308
Banerjee M.....	61	Buick RJ.....	335, 338, 364, 365	Dalla-Favera R.....	38, 56, 102, 288, 356
Bank A.....	154	Bunn HF.....	234	Dalton A.....	320
Bank-Schlegel S.....	369	Buach H.....	418	Danjo Y.....	283
Barker PE.....	289	Buach M.....	325	Daide JP.....	379
Barrois M.....	349	Caccia NC.....	129	Davis KE.....	252
Barth R.....	89	Caillan R.....	365	Davis T.....	168
Bartram C.....	159	Caimi PG.....	77	Davis M.....	14, 28, 30, 31, 207
Bartram CR.....	141, 147, 148, 153, 160, 161, 168, 169, 171, 178, 182, 414	Cairncross JG.....	364	Davis MM.....	255
Battay J.....	7, 8, 22, 23, 24, 25, 26, 27, 46, 131, 267, 292, 330	Calabi F.....	63, 87	Davis RL.....	144
Battay JF.....	309	Calame K.....	76, 89	Dayton AI.....	228
Battifora H.....	269, 359	Calderon-Soli L.....	180	De Brackeleer M.....	409
Bauer SR.....	65, 204	Calza RE.....	100	De Jong B.....	202
Baumgartner J.....	59, 81	Canaani E.....	146, 150, 158, 162, 200, 201	De Klein A.....	141, 147, 149, 151, 152, 159, 161, 168, 169, 171, 182
Baylin SB.....	355	Cannani E.....	177	De Leij L.....	202
Bazin H.....	88	Cannizzaro L.....	167	De Martinville B.....	191, 194, 346
Beard ME.....	140	Carbonell F.....	141	De Taine C.....	213
Benedict WF.....	327, 347	Care A.....	97, 98	De la Chapelle A.....	116, 257, 281, 358
Benjamin D.....	43	Carney DN.....	276, 292, 299, 303, 309	DeBortoli ME.....	344
Berdichevsky FB.....	383	Carritt B.....	241	DeJesus E.....	17
Berger MP.....	184	Carstensen A.....	68	Dean M.....	82
Berger R.....	13, 94, 197, 213, 257	Cassingsa R.....	279	DelGiudice T.....	100
Bergh J.....	277	Castagna M.....	12	Dery C.....	66
Bernard O.....	33, 49	Caubet JF.....	94, 197		
		Chaganti RS.....	16, 54, 163, 179, 193, 227, 278		
		Champlin R.....	243		
		Chang CM.....	290		

AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS
Derynck R.	15	Gandar AF.	303, 309, 330	Harsh G.	268
DiPaolo JA.	189, 399	Gee CE.	324	Hart I.	93
Diaz M.	196	Gegonne A.	213	Hart J.	254
Diaz MO.	156, 195, 238, 239	Gelmann EP.	40	Hartman KD.	274
Diehl RE.	36	Gemmell RM.	172	Harvey T.	58
Donlon T.	278, 313	George D.	285, 352	Hasleton PS.	332
Dorney DJ.	228, 345	George DL.	345, 346	Hatanaka M.	138
Dosik H.	149, 155	Gerondakis S.	33, 49, 71, 83, 85	Hayashi K.	291, 294, 342, 351
Douc-Rasy S.	273	Geurts van Kessel A.	168	Hayashi Y.	311
Drabkin HA.	93, 195, 196, 246	Giacalone J.	194	Hayday AC.	34, 96, 103
Drabkin HD.	211	Giallongo A.	142, 188	Hayflick JS.	572
Drwings HL.	39	Giampacolo A.	97, 98	Hayward WS.	34, 54, 95, 96, 103, 163, 193, 405
Dryja T.	278	Gibas Z.	259	Heaton DC.	140
Dubouzet J.	185	Gilbert F.	265, 304, 329, 382, 395	Hecht BK.	172, 222
Duby AD.	209	Gill GN.	368	Hecht F.	172, 222
Duesberg PH.	212, 398	Gillies SD.	96	Hedberg T.	280
Dugan D.	17	Giovanazzo B.	223	Heighway J.	332
Dull TJ.	372	Givol D.	200, 201, 235, 236, 411	Heikkila E.	164
Dunnick W.	59, 81, 86	Glanville N.	373	Heilman CA.	52
Dutronquay V.	349	Glazer RI.	274	Heim S.	157
Dyson PJ.	9, 10	Glick B.	345	Heintz NH.	388
Eckhardt LA.	72, 100	Glick MC.	319	Heisterkamp N.	147, 149, 151, 159, 161, 169, 171, 182, 240, 241
Eddy RL.	209	Godal T.	280	Henderson AS.	288
Eisenman RN.	300	Godde-Salz E.	152	Henglein B.	35
Ellis KP.	252	Gol R.	192, 412	Hennighausen L.	8, 26, 27
Ellis RW.	354	Golde DW.	243	Herlyn M.	229
Ellison J.	325	Goldfarb MP.	321	Hester J.	139
Emanoil-Ravier R.	337	Goldman JM.	298	Hiorns LR.	240
Emanuel B.	37, 111	Goldman P.	7, 216	Hirai H.	339
Emanuel BS.	16, 115, 137, 167, 210, 223, 228, 235, 302, 319	Goldstein M.	304	Hirohashi S.	334, 350
Epstein AL.	216	Goldstein S.	341	Hoggan MD.	187
Erikson J.	4, 5, 6, 17, 18, 19, 21, 37, 38, 39, 41, 42, 43, 50, 51, 56, 57, 67, 102, 111, 115, 119, 123, 137, 167, 206, 207, 210, 218, 223, 225	Goodfellow PN.	240, 241	Hollings PE.	140
Erismann MD.	36	Gopal TV.	234	Hollis GF.	22, 24, 181, 330
Eva A.	412	Gordon H.	403	Hoo JJ.	164
Evan GI.	301	Gordon L.	221	Hood L.	75, 89
Evans HJ.	47	Gorham J.	215, 219	Hosogai K.	350
Evans RM.	368	Gowda SD.	270	Hoxie J.	137
Fahrlander PD.	60, 70, 78, 80, 284	Goyns MH.	186	Hsiao WL.	199
Falda M.	223	Graham KA.	338	Hu CP.	290
Feenstra A.	200	Graham M.	66	Huebner K.	3, 5, 6
Feinberg A.	268	Graham SV.	271, 298	Hughes D.	99
Feo S.	3, 58	Gray A.	372	Hunts JH.	366
Ferguson-Smith MA.	168	Griffin CA.	137, 355	Ichimaru M.	220
Films J.	364, 365	Grignani F.	174	Ikawa S.	360
Films JE.	335	Groffen J.	147, 149, 151, 156, 159, 161, 169, 171, 182, 240, 241	Iivonen M.	281
Finan J.	3, 19, 37, 38, 42, 57, 111, 119, 137, 206, 218, 228, 302	Grossman A.	319	Ingvorsen S.	68
Finan JB.	115	Grosso LE.	275	Ise T.	311
Finger LR.	224	Grosveld G.	141, 147, 149, 151, 153, 159, 161, 168, 169, 171, 182	Ishii S.	367, 399, 371
Fitzgerald PH.	140	Grosveld GC.	152	Isobe M.	207, 210, 235
Flandrin G.	13	Groudine M.	307	Israel MA.	318
Foon KA.	243	Groudine MT.	166	Jaffe E.	214, 215, 219
Ford E.	345	Grzeschik KH.	328	Jakovovits A.	322
Forster A.	2, 10, 29, 30, 31, 45, 170	Guerin M.	272	Januszewicz E.	162
Franklin L.	59, 81	Guerts van Kessel AH.	211	Jarrett O.	99
Franchini G.	205	Gutterman J.	91, 139, 143	Jaspers NG.	410
Francis GE.	183	Haber M.	401	Jeanteur P.	64
Frankie U.	15, 191, 194, 230, 346	Hagemeyer A.	171	Jensen JP.	216
Freese UK.	35	Hagemeyer A.	141, 152, 160, 168, 176, 182, 211	Jhanwar S.	16
Fruscalzo A.	198	Halbrecht I.	254	Jhanwar SC.	54, 163, 193, 227
Fujii G.	376	Haley BE.	344	Johnson B.	292
Fujisawa M.	339	Hall A.	417	Joseph SF.	402
Fujita J.	340	Halsey H.	286	Kaji H.	4
Fushimi M.	334, 350	Hameister H.	35	Kakinuma M.	283
Gale RP.	146, 150, 158, 162, 177, 243	Hamlin JL.	388	Kakizoe T.	351
Gallie BL.	380	Hamlyn P.	29	Kamata N.	363
Gallo R.	91	Hamlyn PH.	31, 44, 45, 48	Kanda N.	278, 311, 329
Gallo RC.	56, 102, 104, 188, 205, 302, 308	Hammond D.	320	Kaufman RJ.	394
Gamou S.	368	Han SH.	290	Kawai S.	362
Gastaldi R.	97, 98	Hanania N.	12	Keath EJ.	73, 90
Gatti RA.	255	Hann SR.	300	Kelekar A.	73
Gattoni-Celli S.	199	Hansen PF.	169	Kelly K.	25, 108
Gazdar A.	292	Harel J.	12	Kemeny JL.	273
		Harper ME.	205	Kenna M.	286
		Harris LJ.	41, 72	Kent RB.	82

AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS
Kersey J.	211	Lewis WH.	208	Mise K.	232
Keski-Oja J.	281	Li FP.	93	Mitchell KP.	22, 24
King CR.	361	Libermann TA.	370, 372	Mitselman F.	157, 262
Kinoshita K.	220	Lifshitz B.	150	Miyahara K.	113
Kinzler K.	266, 378	Lin C.	368	Miyajima N.	360
Kinzler KW.	310	Lin CC.	164, 285, 306, 358	Miyaki M.	336
Kirsch J.	55	Lin LH.	290	Mizuki K.	342
Kirsch IR.	181, 330	Lindgren V.	191	Modjtahedi N.	279
Kiselev LL.	375	Linevsky J.	274	Mohandas T.	231, 237
Kiselev LL.	383	Little C.	292	Monier R.	279
Klar D.	254	Little CD.	303	Montgomery KT.	293, 379
Kleibauer E.	141, 147	Littlefield JW.	415	Moore DE.	192
Klein E.	110, 124, 396	Littlewood TD.	10	Morreau-Gachelin F.	348
Klein G..1, 61, 68, 70, 79, 88, 110, 117, 124, 129, 132, 135, 136, 280, 396		Love J.	205	Morgan R.	222
Klempner KH.	304	Lowry DR.	353, 354	Mori M.	294
Klimanis L.	192	Lueders K.	200	Mori S.	376
Kloetzer W.	143	Lui WY.	290	Mori T.	336
Klotz JL.	75	Ma DP.	367	Morpargo G.	106
Knode MC.	274	Maeda S.	138	Morris CM.	140
Knutsen T.	367	Magrath I.	43	Morton C.	55
Knuutila S.	281, 357	Maguire RT.	52	Morton CC.	209
Koda T.	283	Mak TW.	129, 208	Mougeau E.	101
Koeffler HP.	237, 317	Makino R.	291	Moulding C.	7, 22, 23, 46, 131
Kohl NE.	321, 324, 329	Malcolm S.	14, 28, 30, 31	Moxley M.	47
Koike K.	389	Malera PW.	391	Munke M.	191
Koike M.	336	Mandahl N.	157	Murao S.	138
Koler RD.	270	Manolov G.	1	Murphree AL.	327
Konopka JB.	142, 144, 145, 165, 173	Manolova Y.	1	Murphy E.	139
Korf B.	313	Marcu KB..41, 60, 64, 65, 70, 72, 78, 80, 84, 104, 284		Murphy W.	23, 46, 131
Korameyer SJ.	216	Mark C.	347	Mushinski JF.	65, 67, 80, 122, 127, 203, 204
Kosaki G.	336	Marshall CJ.	331	Nakano F.	294
Kozak CA.	187	Martin GR.	322	Nakatani H.	316
Kozbor D.	142, 295	Martinotti S.	102	Nakatani K.	294
Kraus MH.	340, 361	Martinson T.	287	Naura H.	113
Kris R.	370	Marx JL.	385	Nash WG.	234
Kristofferson U.	157	Mashal R.	268	Nau MM.	292, 299, 303, 309, 330
Kuff EL.	200	Mastroberardino G.	97, 98	Naylor SL.	53, 231, 328
Kurzrock R.	143	Mathieu-Mahul D.	13, 94, 197	Neel BG.	54, 163, 193
Kusano M.	220	Matsui T.	336	Negishi M.	319
Lacey SW.	105	Matsushim: S.	283	Neil JC.	99
Lacombe MJ.	272	Matthews JG.	170, 248	Nepveu A.	284
Laiho M.	281	Mauchauffe M.	13	Neri G.	121
Lalley PA.	53	Mavilio F.	97, 98	Neuberger MS.	63, 87
Land H.	32	Mazabraud A.	185	Nichols WW.	249
Lander MR.	354	McBride OW.	192, 216, 236, 330	Nicoli J.	423
Landin RM.	279	McCarthy DM.	298	Nienhuis AW.	234
Lane MA.	416	McCoy MS.	353	Nilsson K.	277
Lanfrancione L.	288, 356	McCredie K.	91	Nilsson MG.	61, 280
Larizza L.	260	McFarlane R.	99	Niemi PD.	321
Larsen CJ.	13, 94, 197	McIntosh RV.	47	Nilan M.	294
Latt S.	25, 278	McWilliams-Smith MJ.	212	Nishikura K.	4, 5, 6, 17, 18, 20, 37, 42, 50, 51
Latt SA.	313, 329	Mears J.	154	Nishizura S.	350
Lavialle C.	279	Melera PW.	293, 323, 379	Nishino K.	220
Lavu S.	203	Mellstedt H.	280	Nishizawa M.	232
Laws G.	228	Meltzer P.	268, 378	Nomura N.	360
Lax I.	370	Meltzer PS.	310	Norris JS.	341
Le Beau M.	226	Mercola M.	76	Nose K.	342
Le Beau MM.	156, 195, 196, 238, 239, 242	Merlino GT.	366, 367, 369, 371	Nowell P.	38, 123, 302
Le Fevre C.	269	Merry D.	236	Nowell PC..3, 16, 19, 37, 39, 42, 57, 111, 115, 118, 119, 137, 167, 206, 210, 218, 219, 223, 224, 225, 228, 229	
Leder P..7, 8, 22, 23, 24, 25, 26, 27, 46, 55, 107, 109, 131		Mesander G.	202	Nunn MF.	212
Lee J.	372	Mett VL.	383	Nusbaum HR.	370
Lee WH.	327	Meyer G.	423	O'Brien SJ.	212, 234
Lees G.	99	Michalevicz R.	183	Odajima T.	180
Lehto VP.	277	Michalopoulos EE.	208	Ohno S.	69
Leibowitz D.	154	Michitach RW.	293, 323, 379	Okabe T.	339
Lemieux L.	101	Mihara K.	138	Okamoto H.	342
Lenoir G.	1, 37, 46, 55, 131, 135, 184	Milbrandt JD.	388	Onions LE.	99
Lenoir GM.	7, 23, 24, 25, 32, 42	Miller AD.	377	Onorato-Shove L.	225
Lenore GM.	35	Miller C.	237	Oosterhuis TW.	202
Leonard A.	79	Miller DA.	67	Oren M.	235, 238
Leprince D.	357	Miller OJ.	67	Orta G.	349
Levan A.	1, 287	Minden MD.	208, 338	Peng FK.	290
Levan G.	88, 287	Ming J.	207	Pali ML.	393
Levinson AD.	305	Minna JD.	292, 299, 303, 309, 330		

AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS
Palumbo A.	167, 207, 223	Rovigatti U.	374	Simizu K.	343
Papa TS.	40, 211, 212	Rovigatti UG.	36, 296, 297	Simon MI.	205
Parada LF.	32	Rowley JD.	126, 133, 134, 156, 175, 195, 196, 221, 226, 238, 239, 242, 251, 266, 424	Singer JW.	145
Park M.	198	Ruddle F.	75	Sklar J.	217
Parmiter A.	319	Ruddle FH.	259	Skurka RM.	67
Parmiter AH.	229	Rupniewska ZM.	245	Sleijfer DT.	202
Pastan I.	366, 367, 371	Sacchi N.	211	Smit EM.	152, 160
Patterson P.	56, 93, 193, 196, 211	Sadamori N.	220	Smith DH.	305
Pearson M.	175	Sager R.	404	Smith L.	143
Pegoraro L.	223	Saito H.	34, 96, 103	Smith SD.	222
Pellici PG.	356	Saito T.	360	Solomon E.	226, 240, 241
Peries J.	337	Sakaguchi AY.	53, 231, 328	Solt DB.	180
Perlman C.	280	Sakai K.	278, 313	Sonenshein GE.	82
Perlmutter RM.	75	Sakaki MS.	407	Soreq H.	370
Peracho M.	333	Sakamoto H.	294, 316	Sparkes RS.	255
Peschle C.	97, 98	Sakazaki K.	277, 281	Spengler BA.	391
Philip I.	184	Sakuma S.	420	Spiller M.	143
Philip T.	184	Sakurai M.	244	Spira J.	61, 88, 258
Phillips RA.	380	San Roman C.	226	Spow NM.	97, 98
Piccoli SP.	77, 90	Sandberg AA.	125, 172, 253, 259, 263	Spurr NK.	171, 241
Pisachczyk M.	60, 64	Sasaki A.	283	Squire J.	360
Pimentel E.	406	Sasaki M.	232	Srivastava A.	341
Pitot HC.	275	Sasaki MS.	261	Srivastava SK.	340
Pollak MN.	364, 365	Sather H.	320	Stam K.	149, 151
Popenoe DW.	154	Sato C.	336	Stamberg J.	181
Popescu NC.	189, 399	Sausville E.	330	Stanbridge EJ.	347
Potter H.	24, 46, 131	Sausville EA.	267, 309	Stanley KF.	240
Potter M.	79, 122, 127, 128, 203, 204	Schaefer-Rego K.	154	Stetson LW.	41, 72, 78, 80, 84, 104
Poupon MF.	279	Schafer R.	419	Stark GR.	584
Povey S.	240	Schildkraut CL.	100	Steel CM.	47
Prasolov VS.	375	Schimke RT.	387, 392, 394	Stehelin D.	213, 357
Prasolov VS.	583	Schirmacher V.	260	Steiner-Saltz D.	162
Pravicheva D.	75	Schlesinger J.	370, 372	Stephenson JR.	159, 161, 169, 171, 240, 241
Prelm J.	76, 89	Schraffordt Koops H.	202	Stewart BW.	401
Prokocimer M.	237	Schreck R.	278	Stewart T.	46, 131
Psallidopoulos MC.	40	Schreck RP.	313, 329	Stinson MA.	2
Puck J.	207	Schultz C.	59, 81	Stone M.	168
Rabbits PH.	2, 11, 30	Schwab M.	285, 287, 304, 306, 314, 315, 322, 325, 326, 328, 352, 358	Stratton RH.	367
Rabbits TH.	2, 9, 10, 11, 14, 28, 29, 30, 31, 44, 45, 48, 170	Schwarz DF.	181	Strombeck B.	157
Rabin M.	289	Scolnick EM.	354	Su TS.	290
Ramsey G.	287, 301	Scott AF.	345, 346	Sugimura T.	291, 294, 316, 351, 359
Ranyard J.	317	Scotto KW.	379	Sugiyama T.	138
Rapaport A.	7	Sears JF.	187	Sumegi J.	61, 68, 70, 88, 280
Rappold GA.	35	Seeger R.	313	Swallow DM.	240
Ramooi FV.	298	Seeger RC.	310, 312, 315, 320, 326	Swali D.	55
Ramouzarlegan M.	101	Seidman JG.	209	Swan DC.	189, 192
Ratner L.	402	Seifter EJ.	267	Sziper J.	88
RASON N.	370	Seki T.	376	Szurek P.	59
Read H.	47	Sekiya T.	334, 350	Tagawa M.	220
Rechavi G.	200, 201	Selden JR.	16, 167, 228, 302	Tahara E.	316
Reddy EP.	203, 204	Semba K.	232, 360, 363, 371	Taira M.	389
Reeve AE.	140	Shabtai F.	254	Takahashi M.	233
Revoltella RP.	198	Shaoi D.	12	Takahashi R.	138
Reynolds CP.	318	Sheer D.	226, 240	Takai S.	336
Rhim JS.	340	Shell BE.	86	Takaku F.	339
Richardson CL.	338	Shen-Ong GL.	90, 203	Takao S.	294
Richert N.	369	Sheppard DM.	226	Takayama J.	311
Rimbaud C.	185	Sherr CJ.	234	Talpaz M.	139, 143
Riou G.	272, 273, 349	Shibuya M.	282, 376	Tam AW.	372
Ripley S.	288	Shih C.	194	Tamaoki N.	376
Ritz J.	233	Shioh Y.	278, 313	Tambourin P.	348
Robbins KC.	412	Shimizu N.	366, 368	Tantravahi U.	25
Robert-Lezema J.	348	Shinozaki Y.	294, 350	Targovnik H.	289
Robertson M.	130	Shipley J.	278, 313	Taub R.	22, 23, 24, 25, 46, 55, 131
Robins TS.	52	Shmookler Reis RJ.	341	Tavitian A.	348
Roe BA.	367	Showe L.	58	Taya Y.	350
Romsdrenk H.	302	Showe LC.	4, 142	Terada M.	294, 316, 359
Romero P.	139	Showa TB.	209	Terrier P.	273
Rosens W.	325	Shtivelman E.	150	Tesfaye A.	321
Rosenblum M.	268	Sidell N.	317	Tewer PC.	80
Rosenfeld MG.	368	Siebenlist U.	8, 26, 27, 108	Tewer PM.	78
Rothberg PG.	36	Siegel SE.	320	Testa JR.	134
Roder V.	237	Sierzega ME.	142	Testa MG.	97, 98
Rovers G.	50, 51, 104, 137, 167, 207, 223, 302	Sieverts H.	43	Teyssier JR.	147

AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS	AUTHOR	ABSTRACT NUMBERS
Thiele CJ	318	Van Agthoven T	168	Wiener F	61, 68, 70, 79, 127
Thierfelder W	42	Van Boom JH	331	Wilkie NM	99
Thomas OH	181	Van Dalen I	202	Willecke K	419
Thompson DM	368	Van Kessel AG	171	Williams DL	206, 208
Thorgeirsson SS	52	Van Straaten P	11	Wilson RK	367
Tindle RW	271	Van der Eb AJ	331	Wiman K	96, 103
Ting LP	290	Van der Kamp AW	410	Wiman KG	34, 95
Tjio JH	249	Van der Meer I	202	Winqvist R	281, 357, 358
Tobaly J	337	Variakojis D	221	Winter E	333
Tokunaga A	334	Varmus HE	285, 287, 304, 306, 314, 315, 325, 326, 328, 352, 408, 413	Winter J	221
Tonegawa S	34, 96, 103	Vasicek T	23	Wirschbaky Z	68
Tonemura A	336	Vassart G	289	Witte ON	142, 144, 145, 165, 173
Toole JJ	353	Veeneman GH	331	Wolf D	237
Tordjman I	349	Verlaan-de Vries M	331	Wolman SR	288, 356, 422
Toyoshima K	232, 359, 360, 362, 363, 366, 371	Verma IM	377	Wong KY	320
Trent J	268, 304, 328	Verma RS	149, 155	Wong-Staal F	91, 205, 308, 402
Trent JM	310, 338, 378, 381	Vilette D	337	Wood C	96
Tret'jakov LO	375	Vimer M	202	Wright JJ	216
Tret'yakov LD	383	Vogelstein B	268, 310, 378	Xu YH	366, 367, 369, 371
Triche T	43	Wahl GM	384	Yamada Y	220
Tripputi P	228	Wang E	167	Yamaguchi T	138
Tronick S	55	Watanabe SM	145, 165	Yamamoto F	333
Tronick SR	189, 192, 340, 400, 412	Waterfield MD	370	Yamamoto T	232, 359, 360, 362, 363, 366, 371
Trusko S	345	Watson DK	211, 212, 374	Yancopoulos GD	321
Tsachida N	336, 342, 350, 420	Watson J	11	Yander G	286
Tsachida Y	311	Watt R	41, 50, 51, 84, 104	Yang JQ	64, 65, 70, 72, 80, 284
Tsachiya R	350	Watt RA	21	Yang-Feng TL	230
Tsujimoto Y	123, 214, 215, 218, 219, 224, 225	Wax JS	79	Yao E	253
Tsunetsugu-Yokota Y	269	Webb E	33, 49, 66, 74, 85	Yarden Y	372
Tu Z	25	Weber W	368	Yokota J	269, 282, 357
Turc-Carel C	152, 184	Weinberg RA	32, 194, 353	Yoshida MC	232
Turner PH	234	Weinstein IB	199	Yonida TH	421
Tweardy D	207	Weisman BE	347	Yuasa Y	412
Ueshima Y	221	Wendling F	348	Yunis J	224, 225
Uevama Y	282	Westbrook CA	156, 238, 239	Yunis JJ	256, 264, 374, 397
Ullrich A	230, 370, 372	Westin E	91	Zabarovskii ER	375
Urabe A	339	Whang-Peng J	43, 367	Zabarovsky ER	383
Utakoji T	311	Whittle N	370	Zehnbauer BA	310
Valtieri M	137	Wickremasinghe RG	183	Zeliszewski D	12
Van Agthoven AJ	152, 160			Zokas L	377



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